HOSPITAL LIBRARY Property of JAMES
DO NOT REMOVE FROM THIS ROOM

Vol. 31 JULY, 1947 No. 1

THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

BORDEN S. VEEDER
St. Louis
Editor

Published by THE C. V. MOSBY COMPANY, 3207 Washington Blvd., St. Louis 3, U.S.A.
Copyright 1947 By The C. V. Mosby Company

Table of Contents on 3rd Cover

PECTOCEL

(Pectin and Kaolin Compound, Lilly)

'Pectocel' is a nonchalky, attractive kaolin mixture with a creamy, heavy-bodied smoothness. This preparation has considerable appeal to the patient. The ample kaolin content functions as an adsorptive and effectively produces a protective coating that soothes inflamed intestinal mucosa.

'Pectocel' is indicated for the supportive treatment of diarrhea and inflammation associated with enteritis, gastritis, colitis, and other intestinal infections or intoxications.

Formula:

An aromatized aqueous suspension containing in one fluid ounce:

Pectin	4 1/2 grs.
Kaolin	90 grs.
Zinc Phenolsulfonate	1 1/8 grs.

'Pectocel' is available at pharmacies everywhere.

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U. S. A.

Vol. 31, No. 1, July, 1947. The Journal of Pediatrics is published Monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: United States, its possessions, Pan-American Countries, $8.50 a year; Canada, $10.00 (Canadian Currency); Foreign, $9.50. Entered as Second-Class Matter June 29, 1932, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in the U. S. A.

Hou
gt

Hospital
of

The Journal of Pediatrics

VOL. 31 JULY, 1947 NO. 1

Original Communications

ROCKY MOUNTAIN SPOTTED FEVER

A PRELIMINARY REPORT ON THE USE OF PARA-AMINOBENZOIC ACID

CLIFFORD J. TICHENOR, M.D., LIEUTENANT SIDNEY ROSS (J.G.), MEDICAL CORPS, UNITED STATES NAVAL RESERVE, AND PRESTON A. MCLENDON, M.D.
WASHINGTON, D. C.

THE present report deals with the general considerations of thirty-six cases of Rocky Mountain spotted fever observed at The Children's Hospital, Washington, D. C., between 1931 and 1946, and the specific management of eight patients treated in the summer of 1946 with para-aminobenzoic acid.

INTRODUCTION

The identification of the disease in the East by Badger, Dyer, and Rumreich[1] in 1931, was followed by the rapid recognition of its prevalence in the central and eastern states. Since 1940, reports of Rocky Mountain spotted fever have come from almost all over the United States, the total annual incidence of reported cases ranging from 400 to 500. In the East the highest incidence is in Maryland, Virginia, and North Carolina. In the Rocky Mountain and Pacific coast states the wood tick, *Dermacentor andersoni,* is responsible for transmission to man. In the East and South the dog tick, *Dermacentor variabilis* is the important carrier.

The total number of cases in the United States reported for the five years, 1933 to 1937 inclusive, was 2,990, with 420 deaths[2]; of these, 1,435 patients and 273 deaths were from the Mountain and Pacific states, with a death rate of 19.4 per cent. In 1944, there were 470 patients with 130 deaths. The mortality varies greatly but remains fairly constant in different localities. In the Bitter Root Valley, it was over 80 per cent for adults and 27.5 per cent for children. The case fatality rate for the entire United States is about 22 per cent and is influenced by the age of the individual rather than by geographic location. In all regions the disease is much more fatal in adults than in children.

In the sixteen-year series at Children's Hospital there was a mortality rate of 8.3 per cent with three deaths in thirty-six patients. The age incidence of the thirty-six patients ranged from 15 months to 13 years, the average being 5 years. Of these, 61.2 per cent were males and 38.8 per cent females. The

From The Children's Hospital, Washington.

high incidence among males is explained by the playing habits of boys, presenting a greater liability to exposure. In this series, 91.7 per cent were white and 8.3 per cent were colored. Nine, or 25 per cent (including the three deaths), developed complications of which there were five cases of pneumonia, two of otitis media, and two of parotitis.

The seasonal incidence of spotted fever corresponds to the tick seasons of the locality concerned. Of the thirty-six cases, all living in the greater Washington area, there was one case in March, one in April, ten in May, ten in June, eleven in July, and three in August. *D. variabilis* in the East appears in March and is most abundant from May to July, but it is reported that they are found as late as November and December. The history of tick bite was elicited in 69 per cent of these patients and was not considered mandatory for a provisional diagnosis.

SIGNS AND SYMPTOMS

The majority of patients were ill for about a week prior to hospitalization. During the prodromal stage, malaise, chilly sensations, and anorexia were common complaints. The invasive stage was accompanied by variable degrees of prostration, headache, irritability, muscular aches, abdominal pain, vomiting, epistaxis, photophobia, lethargy, meningismus, and rarely by delirium and/or coma. In one instance there was edema of the face, feet, and genitals. The spleen was palpable in 25 per cent of the patients.

In the usual instance the temperature rose rapidly to 102° to 104° F. in the first two to three days and remained elevated during the next ten to fourteen days; thereafter, the fever came down by lysis during the third week so that a normal temperature was reached on an average of eighteen days after the onset of the disease.

The rash usually appeared about the third or fourth day after the onset of fever although on occasion its appearance was delayed until the sixth or seventh day. The eruption appeared first on the extremities and back and rapidly became generalized in centripetal fashion. At first it was in the form of rose-colored, elevated macules, palpable and disappearing on pressure. These macules soon became deep red or purplish in color and increased in size, often becoming confluent; within a few days the rash usually became petechial in character. Cutaneous and subcutaneous hemorrhages of considerable size occurred in 40 per cent (severe cases). In the less severe cases the petechiae remained small and discrete to give a mottling "turkey egg" effect. The rash tended to disappear with the subsidence of the fever.

The laboratory findings were not impressive and offered little help initially. The urine was that of any febrile disease. In the uncomplicated cases there was a slight leucocytosis ranging between 8,000 and 12,000 with a moderate shift to the left of the polymorphonuclear elements. In two patients the white blood counts were 25,000 and 30,000 on admission. No initial leucopenias were found. The red cells decreased in number as the disease progressed and transfusions of whole blood or plasma were required in 17 per cent of the patients.

The Weil-Felix reaction was of considerable value in establishing a diagnosis, but the time relationship for positivity only served to emphasize that the diagnosis was essentially clinical during the most critical stage of the disease. The earliest positive agglutination in this series was six days after the onset of fever; in thirty-four out of thirty-six patients, however, the OX19 agglutination titer was below 1:160 before the twelfth day. In all patients but one the titer was diagnostic (i.e., above 1/160) between the third and fourth week. Titers of 1:5,120 were not unusual. One patient was hospitalized on the second day of fever and discharged on the twelfth hospital day, the Weil-Felix reaction being negative at this time. The patient returned to the outpatient clinic as requested twenty-two days after the onset of fever, at which time the agglutination titer was found positive in the dilution 1:640. It is well to point out that the Weil-Felix may be delayed until early convalescence.

The complement-fixation test with antigen from the yolk sac of the chick embryo was performed in six cases and was positive in all at the beginning of the third week. The Children's Hospital was fortunate in having readily available the facilities of the National Institute of Health for such a specific test.

Spinal punctures were performed on twelve, or 33 per cent, of these patients, because of variable central nervous system signs and symptoms. Of these, five showed a pleocytosis ranging between 19 and 75 cells. Spinal fluid chemistries were normal.

Rocky Mountain spotted fever was considered as one of the diagnostic possibilities in thirty-five of the thirty-six patients on admission to the hospital. This is in keeping with the premise that in an area such as ours where there is an unusual geographic concentration of the disease and where the physician is on the alert for its appearance during the tick season, the diagnosis is usually readily made clinically after the appearance of the rash. Other diagnoses which were entertained included typhoid and typhus fever, measles, and meningococcus meningitis. Blood cultures, Widal reactions, and spinal punctures aided in the differential diagnosis. The outstanding clinical difference was found to be the evolution and distribution of the rash.

MANAGEMENT

Prior to the use of para-aminobenzoic acid, the treatment was largely symptomatic and supportive. Eight patients, prior to 1946, received hyperimmune rabbit serum developed by Topping; none of the eight received serum during the first three days of the disease and none had any perceptible diminution in the severity of their course. Serum sickness occurred in two of these patients. "Immune" blood was tried in one severe case but the patient died. Because of the endarteritis in this disease, intravenous fluids have been thought to be contraindicated[3] until recently when Harrell and associates[4] demonstrated that no ill effects were noted when it became necessary to treat peripheral shock or hypoproteinemia by the intravenous route. Our results are essentially in agreement with their conclusions; no untoward reactions were observed following the administration of blood, plasma, amigen, or crystalloid fluids by the intravenous route in the nine patients in whom it was employed.

Use of Para-Aminobenzoic Acid.—In view of preliminary evidence that para-aminobenzoic acid might be a valuable therapeutic agent in the treatment of rickettsial diseases, it was deemed of considerable interest to attempt to treat Rocky Mountain spotted fever at Children's Hospital in 1946 with this drug.

The deleterious effects observed following the use of sulfonamide drugs in rickettsial infections led Snyder and associates[5] to the conclusion that the antagonism between sulfonamide drugs and para-aminobenzoic acid in bacterial growth might be present in a reverse direction in rickettsial infections, and prompted the investigation of the possible virtues of para-aminobenzoic acid against rickettsiae. These authors found that the mortality from experimentally induced murine typhus in mice was considerably reduced when para-aminobenzoic acid was administered. In their series, 80 per cent of untreated control mice died while 80 per cent of the mice who received para-aminobenzoic acid survived. Similarly, the inhibitory effects of para-aminobenzoic acid in developing chick embryos infected with murine typhus was noted by Hamilton and associates.[6] In the first clinical investigation Yeomans and associates[7] treated 20 patients with louse-borne typhus with para-aminobenzoic acid in Cairo, Egypt, and used alternate patients as controls; the daily dose of the drug ranged between 24 and 28 Gm. and an attempt was made to attain a blood level ranging between 10 to 20 mg. per cent. These investigators noted that the average duration of fever for the forty-four untreated patients was 18.5 days, whereas in twenty patients treated with para-aminobenzoic acid the average duration of fever was 12.5 days. In commenting on their results, Yeomans and associates pointed out that among the group of forty-four untreated patients there was only one mild case and that the fatal cases were 18 per cent of the total, while on the other hand there were eleven mild cases and no deaths in the group who received para-aminobenzoic acid. The average duration of hospital stay for the treated patients numbered twenty-one days while that of the untreated patients was thirty-two days. These authors concluded that para-aminobenzoic acid lessens the severity of louse-borne typhus and emphasized that early initiation of therapy, preferably before the third day, was extremely important.

The extension of clinical and experimental investigation to determine whether para-aminobenzoic acid exerted any rickettsiostatic activity against other types of rickettsia constituted a logical extension of this field of investigation. Tierney[8] treated eighteen patients with tsutsugamushi disease with para-aminobenzoic acid and used sixteen alternate patients as controls. He reported that the great majority of patients receiving para-aminobenzoic acid had mild courses and there were no deaths in this group; of the untreated group, however, three died and seven were critically ill. Tierney concluded that para-aminobenzoic acid exerted a beneficial effect on the course of tsutsugamushi disease and similarly emphasized the importance of early treatment, i.e., before the first week.

Smith,[9] employing a dose of 2 Gm. every two hours, treated twenty-nine patients with endemic typhus and used twenty-nine other patients as controls; the two groups were thought to be roughly comparable on admission. There

was one fatality in each series and this author concluded that patients who received para-aminobenzoic acid progressed more favorably and followed a more benign course than the untreated cases. The duration of fever in the treated cases was 10.3 days while that in the untreated cases was 13.2 days.

Regarding the antirickettsial activity of para-aminobenzoic acid in Rocky Mountain spotted fever, Anigstein and Bader[10] in 1945 demonstrated that when guinea pigs were experimentally inoculated with spotted fever, about 80 per cent of those animals receiving para-aminobenzoic acid recovered while all control animals died. Hamilton[11] reported that para-aminobenzoic acid inhibited spotted fever rickettsia in developing chick embryos to an even greater extent than murine typhus. In the first reported instance of the treatment of Rocky Mountain spotted fever in human beings with para-aminobenzoic acid, Rose and associates[12] discuss its use in a 46-year-old woman; the drug was instituted on the fifth day of the disease in a dose of 4 Gm. initially and 2 Gm. every two hours thereafter. A prompt recovery ensued. The para-aminobenzoic acid blood levels in this case ranged between 6.6 and 18.6 mg. per cent.

During the summer of 1946, all six patients with Rocky Mountain spotted fever diagnosed at Children's Hospital had been treated with para-aminobenzoic acid. Ideally, it would have been desirable to have treated alternate cases with this drug employing the untreated cases as controls. However, the number of subjects were too few to allow any such control series. Two additional cases in adults were treated by one of us (P. A. M.) and will also be described.

Powdered para-aminobenzoic acid was partially dissolved in 5 per cent bicarbonate of soda solution so that 15 c.c. of the mixture contained one gram of para-aminobenzoic acid. This preliminary neutralization lessened gastric irritation and the drug was well tolerated by the patients.

CASE REPORTS

CASE 1.—D. B., a 4-year-old white female, was admitted to Children's Hospital on July 29, 1946, with the complaints of malaise and fever for seven days' duration and a rash of five days' duration.

The child had been perfectly well until one week prior to entry, at which time she was noted to have become listless and feverish. Forty-eight hours after the onset of the fever a rash appeared, which had its initial distribution about the feet and ankles and progressed so that during the next two or three days there was a generalized distribution over the trunk, chest, and upper extremities. Concomitantly, the child complained of headache and muscular aches and pains in the upper and lower extremities and experienced considerable malaise. The appetite was poor and the child vomited on one occasion. The temperature remained elevated during the entire week prior to entry and the child during this interval appeared acutely ill.

The patient resided on a farm near Potomac Mills, Va. Ticks had been noted in this area and during the earlier part of the spring had been observed on the child and removed but none had been noted recently.

The past history and family history were noncontributory to the present illness.

Physical examination at the time of entry revealed a well-developed, well-nourished 4-year-old white girl who appeared acutely ill but in no obvious distress. Her temperature was 104.8° F., the pulse rate 140, and the respiratory rate 40. Her sensorium was clear but she appeared very irritable and was uncooperative. A discrete, maculopapular rash which blanched

on pressure was noted chiefly on the upper and lower extremities and the trunk. There were a few scattered lesions on the palms and soles. No ticks were found in the hairy regions. The posterior cervical, axillary, and inguinal nodes were small and shotty. The neck was supple and Kernig's and Brudzinski signs were negative. The heart and lungs were normal. The liver and spleen were not palpable. The motor and sensory modalities were in good order. Physical examination was otherwise negative.

In view of the clinical findings together with the known concentration of ticks in this area, a provisional diagnosis of Rocky Mountain spotted fever was made.

Laboratory examination revealed a hemoglobin of 10 Gm. with 3.5 million red cells; the white cell count was 8,400 with 55 per cent neutrophiles, and 45 per cent lymphocytes. The urinalysis was essentially negative. Blood culture was negative as was the Wassermann and Kahn. Weil-Felix agglutination test with Proteus OX19 on July 29, eight days after the onset of illness, was positive in a dilution of 1:20. Five days later the titer had risen to 1:640.

Throughout the first two days in the hospital the child remained acutely ill with the temperature spiking between 100° and 104.5° F. Drowsiness and irritability were marked and the child's appetite remained poor. The rash had become more petechial, and involved the entire thorax and abdomen. During this time supportive measures including antipyretics and an intravenous infusion of 300 c.c. of 5 per cent glucose in saline were administered.

On July 31, forty-eight hours after admission, para-aminobenzoic acid therapy was started. The dose was 3 Gm. initially and then 1½ Gm. every two hours thereafter. On the following day, the dose of para-aminobenzoic acid was reduced to 1 Gm. every two hours, and this dosage was maintained throughout the remainder of therapy. Frequent para-aminobenzoic acid blood levels were taken one hour following the previous dose and revealed the blood level to range between 16 and 24 mg. per cent (Chart 1).

Two days following initiation of para-aminobenzoic acid therapy a rather definite improvement was noted. The patient appeared less toxic, was considerably more alert and her appetite improved. However, the temperature continued to spike during the next five days, ranging between 100° and 102° F. On the sixth day of para-aminobenzoic acid therapy the temperature dropped rapidly to normal. By this time the rash had already begun to fade and the patient was asymptomatic. The child remained afebrile during the remainder of her hospital course. Her recovery was complete and she was discharged on the seventeenth hospital day after an uneventful convalescence.

Para-aminobenzoic acid had been administered for ten days, during which time the child received a total of 110 Gm.

Daily white counts obtained during the course of drug therapy to determine its leucopenic effect revealed a definite granulocytopenia and leucopenia one week after the initiation of para-aminobenzoic acid therapy; the white count at this time was 3,500 with 16 per cent neutrophiles. However, the white count rapidly returned to normal when the para-aminobenzoic acid was discontinued. Hepatic function tests obtained during the course of para-aminobenzoic acid therapy showed a prothrombin time of 50 per cent of normal, total protein of 6.9 Gm. per cent and a 4+ cephalin flocculation test.

CASE 2.—S. H., a 7-year-old white male, was admitted to Children's Hospital on June 30, 1946, with the chief complaint of fever of six days' duration and rash of two days' duration.

The child had been in good health until one week prior to entry, at which time a temperature elevation was observed. The temperature remained elevated during the whole week prior to entry and during this time the patient was rather listless, irritable and showed some degree of anorexia. Two days prior to entry, a maculopapular rash was noted which started on the extremities and then extended centripetally to involve the trunk and thorax. There had been no instance of tick bites as far as known.

The past history and family history were noncontributory.

Physical examination revealed a well-developed child who appeared moderately apprehensive but not acutely ill. Positive findings included a fine maculopapular rash on the face

and extremities with a minimal number of lesions on the body; a few of the lesions were petechial in character. There was a moderate degree of cervical adenopathy and mild conjunctivitis. The liver and spleen were barely palpable. There was a moderate degree of meningismus present with 2+ nuchal rigidity and positive Kernig and Brudzinski signs. Temperature was 104° F., pulse 100, respirations 33. The physical examination was otherwise not remarkable. A provisional diagnosis of Rocky Mountain spotted fever was made.

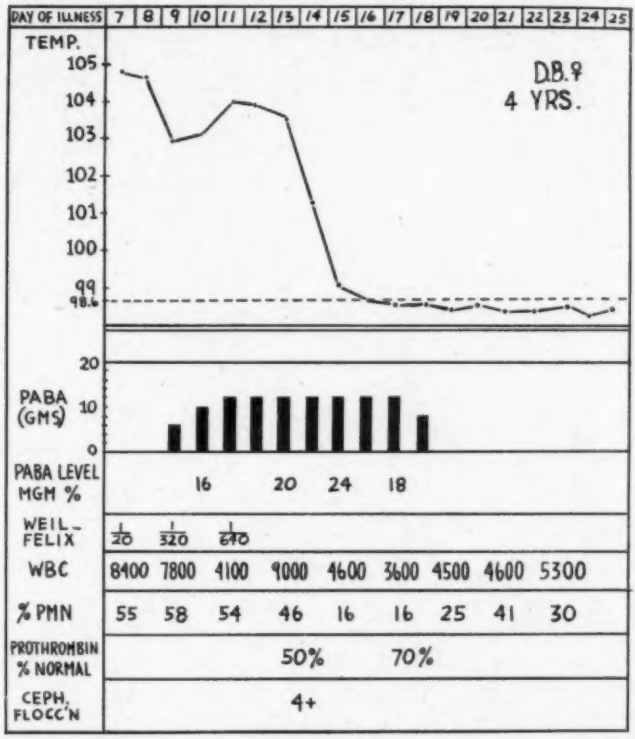


CHART 1

The laboratory examination showed a hemoglobin of 11 Gm. with 3.56 million red cells; the white cell count was 7,350 with 79 per cent neutrophiles, 19 per cent lymphocytes, and 2 per cent monocytes. The urinalysis was negative. Blood culture and spinal fluid examination were negative. Weil-Felix agglutination test with Proteus OX19 was done on June 30, seven days after the onset of illness, and was negative. Ten days later the titer had risen to 1:2,560 and a complement fixation test was positive in a dilution of 1:128.

On the day following admission, para-aminobenzoic acid therapy was started with a dosage of 2 Gm. every two hours, and this dosage was maintained for the next ten days, during which time the patient received a total of 220 Gm. of the drug. Supportive therapy consisted of a high protein intake with adequate vitamin supplements; no intravenous fluids were administered. Frequent para-aminobenzoic acid determinations revealed the blood level to range between 20 and 46.6 mg. per cent.

One day after therapy was begun the child appeared somewhat improved clinically with less hyperesthesia and some improvement in appetite was noted. The temperature continued to spike during the next four days but concomitantly there was a gradual defervescence of fever noted during this time (Chart 2). On the fifth day after therapy was begun, the temperature had returned to normal, the meningismus had disappeared and the rash had begun to fade. The patient was discharged after an uneventful convalescence on the twelfth day. No leucopenia resulting from para-aminobenzoic acid therapy was observed.

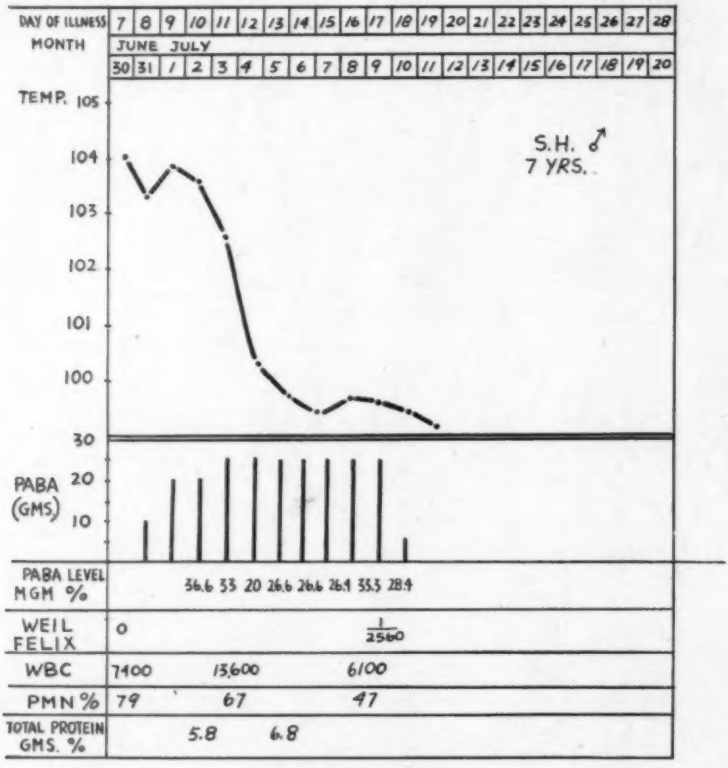


CHART 2

CASE 3.—D. V., a 16-month-old white female, was admitted to Children's Hospital on Aug. 8, 1946, with a history of a tick bite six days prior to admission. The child seemed well until one day before entry, at which time she appeared irritable and fever was observed. On the day of admission a maculopapular rash was noted on the extremities and the abdomen. The past history and family history were noncontributory.

Physical examination revealed a well-developed, irritable child who appeared acutely ill. A diffuse, pale pink, maculopapular, spotted eruption was noted over the entire body, including the face and extremities. A moderate degree of conjunctivitis was noted. The liver and spleen were not palpable, and no meningismus was elicited.

Laboratory examination revealed a hemoglobin of 10 Gm.; the white cell count was 10,600 with 58 per cent neutrophiles, 38 per cent lymphocytes, and four per cent monocytes.

The urine was negative and the blood culture was sterile. The Weil-Felix agglutination test with Proteus OX19 on August 9, three days after the onset of the illness, was negative; eight days later the titer had risen to 1:80 and a repeat agglutination test twenty-two days after admission showed a titer of 1:640. The total protein was 6.5 Gm. per cent and the prothrombin time was 70 per cent of normal. The cephalin flocculation test six days after entry was 3+.

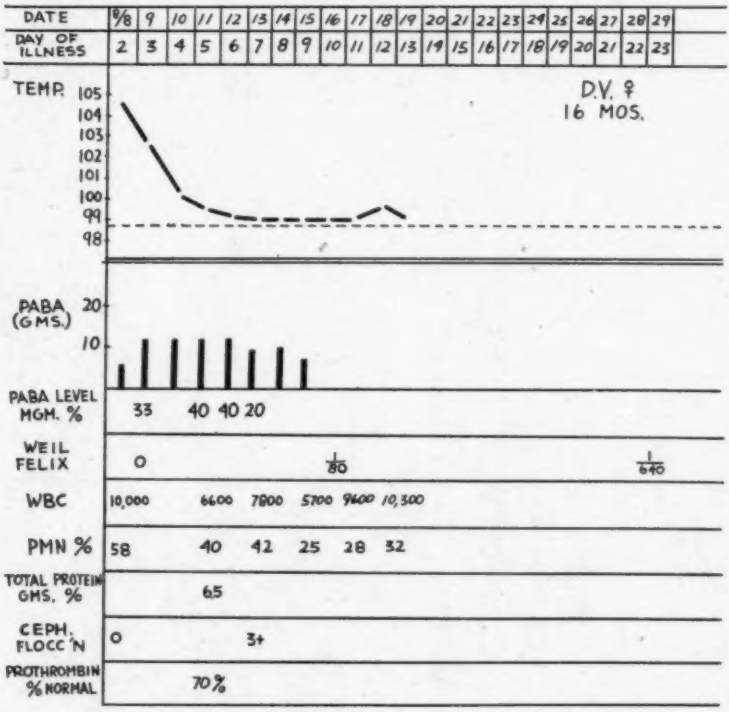


CHART 3

On the day of admission, para-aminobenzoic acid therapy in a dose of 2 Gm. initially and one gram every two hours thereafter was started and this dosage was maintained throughout the remainder of therapy. The drug was continued for eight days, during which time the child received a total of 74 Gm. Repeat para-aminobenzoic acid blood levels obtained during therapy showed a level ranging between 20 and 40 mg. per cent.

Within forty-eight hours after initiation of therapy the temperature dropped precipitously to normal and the child remained afebrile during the remainder of her hospital stay (Chart 3). Coincident with the drop in temperature, the patient's clinical improvement was noteworthy and the rash began to fade on the fifth hospital day. The child was discharged on the twelfth day after an uneventful convalescence.

A slight leucopenic effect was observed on the seventh day of therapy, the white cells dropping to 5,700 with 25 per cent polymorphonuclears; the white count promptly rose to 9,600 two days following termination of therapy.

CASE 4.—S. W., a 9-year-old Negro male, was admitted to Children's Hospital on July 21, 1946, with the chief complaints of fever and listlessness of one week's duration and a rash of four days' duration.

The child was well until one week prior to entry, at which time he began to run a fever and seemed unduly fatigued. At this time he was seen by a private physician and was given sulfadiazine for an indeterminate period. The temperature remained elevated during the entire week prior to entry. Four days after the onset of fever, a rash appeared, which had its initial distribution about the upper and lower extremities. Associated complaints included headache, anorexia, muscular aches and pains in the upper and lower extremities. There was no definite history of tick bite elicited.

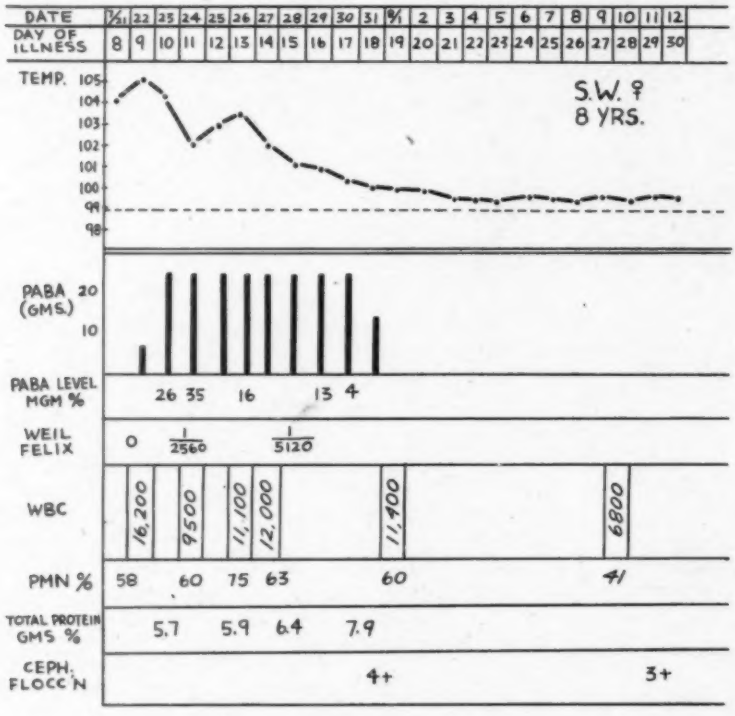


CHART 4

Physical examination revealed a well-developed, poorly-nourished, Negro male who appeared acutely ill. There was a faint maculopapular and petechial rash diffusely distributed over the trunk and abdomen. No nuchal rigidity or cervical adenopathy was noted. The pharynx was markedly inflamed and the tonsils were enlarged and cryptic. The spleen and liver were both palpable about 1 fingerbreadth below the costal margin. The Brudzinski sign was positive bilaterally and the deep reflexes were absent. Temperature was 103.2° F., pulse 140, and respirations 40.

Laboratory examination revealed a hemoglobin of 9 Gm. with 3 million red cells; the white cell count was 16,200 with 58 per cent neutrophiles and 32 per cent lymphocytes. Urinaly-

sis showed 120 mg. of albumin with an occasional hyaline cast; however, repeat subsequent urines were negative. A blood culture was negative. Spinal fluid examination revealed sixty white cells with 40 per cent neutrophiles and 60 per cent lymphocytes; the spinal fluid sugar and protein were within normal limits. Total protein was 5.66 Gm. per cent and the cephalin flocculation test was 4+. The Weil-Felix agglutination test with Proteus OX19 on the second day after entry (nine days after the onset of illness) was negative. However, three days later the titer had risen to 1:2,560 and within another five days a further rise to 1:5,120 was noted; the complement fixation test for Rocky Mountain spotted fever at this time was 1:640.

On the day of admission, the patient was started on penicillin therapy, 50,000 units every three hours intramuscularly. On the following day, however, the child appeared considerably worse; the temperature had risen to 105° F., a definite petechial rash was observed on the hands and feet, and the child appeared semicomatose. On the second day, sulfadiazine was administered by clysis but was discontinued within twenty-four hours when the diagnosis of Rocky Mountain spotted fever became more apparent.

On the third hospital day, or ten days after the onset of the disease, para-aminobenzoic acid therapy was begun (Chart 4). The dosage was 3 Gm. every three hours or 24 Gm. per day and drug therapy was maintained for nine days for a total of 187 Gm. The para-aminobenzoic acid level ranged between 4 and 35 mg. per cent. Supportive therapy included blood transfusions as well as crystalloids and amigen infusions.

Within three days after para-aminobenzoic acid therapy was started, the patient showed some improvement; his sensorium began to clear somewhat and the child appeared to be more responsive to his surroundings. During the first six days after the initiation of the drug, however, the temperature remained constantly elevated ranging between 101° to 102° F. The fever came down by lysis thereafter and during the second week remained around 100° F. Within eleven days after the onset of therapy, the temperature had come down to normal, the total duration of fever being nineteen days. He was discharged after a complete recovery on the thirtieth hospital day.

No leucopenic effect was observed during the course of therapy.

CASE 5.—J. L. M., a 4-year-old white male, was admitted to the hospital on the eighth day after the onset of his illness. The temperature on admission was 104.5° F. and the child appeared quite toxic and dehydrated. There was a diffuse, petechial rash covering the extremities and trunk. A clinical diagnosis of Rocky Mountain spotted fever was made and subsequently confirmed by a Weil-Felix agglutination titer of 1/2,560.

Para-aminobenzoic acid therapy was begun on the day of admission with an initial dose of 3 Gm. and 1½ Gm. every three hours thereafter. Some improvement was noted during the next three days while on therapy, the temperature dropping to normal during this interval. However, on the fourth hospital day, the patient became mildly incoherent and confused and a moderate degree of periorbital and peripheral edema was observed. Concomitantly the temperature again rose and the child appeared definitely worse (Chart 5). The para-aminobenzoic acid blood level ranged between 53 and 80 mg. per cent at this time, and because of the uncertainty regarding the possible toxic effects of the drug as a contributing cause, it was discontinued. Shortly thereafter the child became comatose with evidence of peripheral shock. On the eighth hospital day, a bilateral parotid swelling was observed; at this time a history of possible exposure to mumps two weeks prior to entry was elicited from the parents. A spinal tap was performed on the following day and was negative. Two days later, definite evidence of the right lower lobe pneumonia was demonstrable both on physical examination and on x-ray.

The patient's condition remained critical during the next few days, during which time the temperature fluctuated between 102 and 104° F., and the rash became markedly hemorrhagic and diffuse. Supportive therapy consisted of penicillin, oxygen, and intravenous infusions of crystalloids and blood. Improvement was gradual but progressive and the tem-

perature came down by lysis during the course of the next two weeks. The child was discharged on the thirty-second hospital day after a complete recovery.

No leucopenic effect was observed during the time para-aminobenzoic acid was administered.

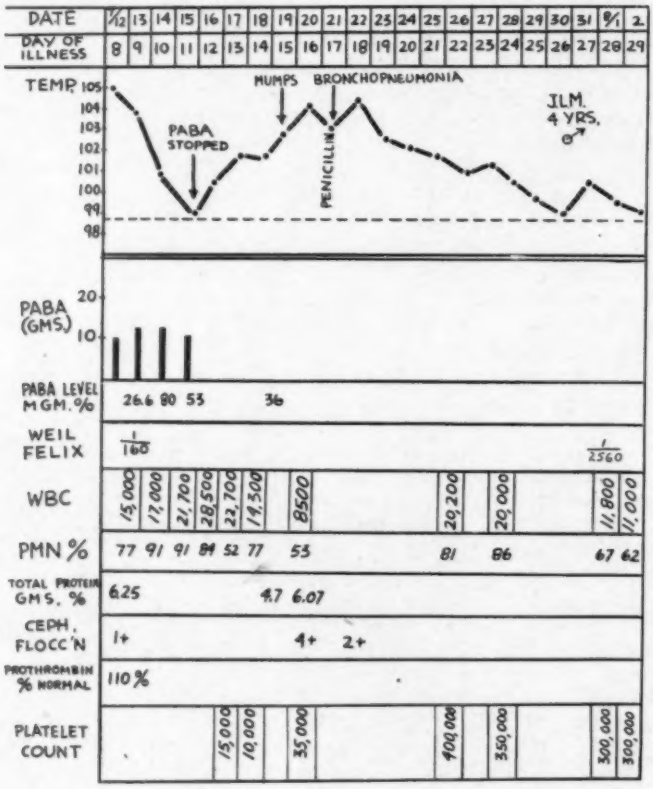


CHART 5

Case 6.—C. C., an acutely ill, 11-year-old white male, was admitted to the hospital on the sixth day of his illness with clinical findings suggestive of a diagnosis of tick fever; a Weil-Felix agglutination titer of 1/2,560 was subsequently obtained (Chart 6). Para-aminobenzoic acid therapy was started on the third hospital day, or eight days after the onset of the disease, in a dosage of one gram every two hours; two days later, the dose of para-aminobenzoic acid was increased to 2 Gm. every two hours because of the relatively low para-aminobenzoic acid blood level (3.4 mg. per cent). The blood level rose on the following day and ranged between 27 and 40 mg. per cent, prompting a return to the original dosage schedule during the remainder of therapy. In all, para-aminobenzoic acid was maintained for nine days, during which time 104 Gm. of the drug were administered.

During the first five days of therapy the patient showed progressive improvement. The temperature, which on entry was 104° F., came down by lysis, and the child appeared con-

siderably less toxic. However, on the sixth day, the temperature again rose to 103° F. and the child appeared quite disoriented and semicomatose. A bilateral, tender, parotid swelling and edematous Stenson's duct at this time was noted and on close questioning of the parents, a history of exposure to mumps ten days prior to admission was obtained. A spinal tap showed 36 white blood cells with 60 per cent polymorphonuclears and 40 per cent lymphocytes; the

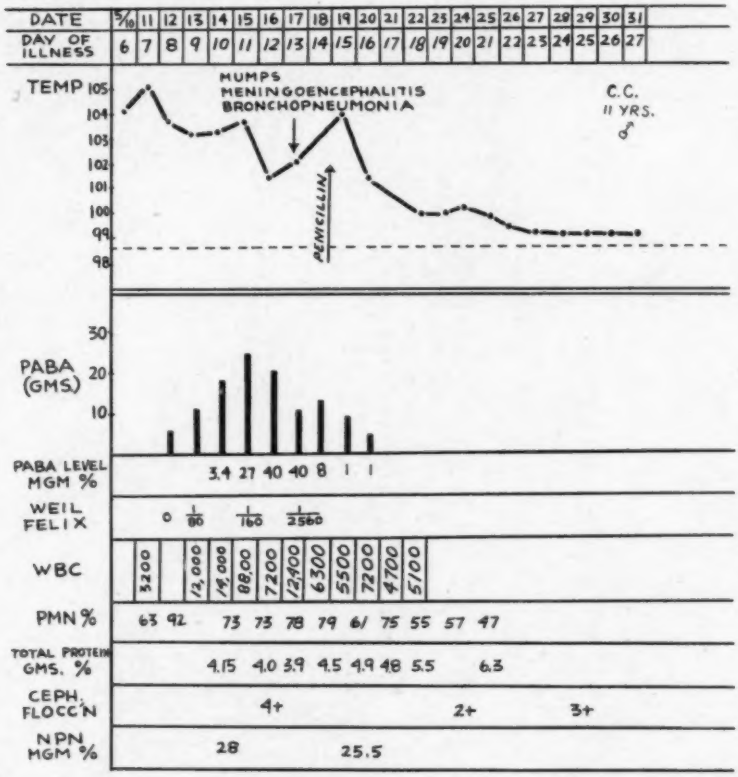


CHART 6

sugar and protein were within normal limits. Spinal fluid findings were interpreted as evidence of a complicating mumps meningoencephalitis. The possibility that the spinal fluid pleocytosis was related to the tick fever rather than mumps was thought to be unlikely in view of the normal lumbar puncture findings noted at the time of admission to the hospital. A complement fixation test for mumps virus subsequently performed at the National Institute of Health was positive.

On the eighth day the temperature rose to 103.8° F. and definite signs of left lower lobe pneumonia were observed; penicillin therapy was therefore initiated while para-aminobenzoic acid was discontinued. Definite improvement was observed during the next five days with noticeable clearing of the sensorium, defervescence of temperature and resolution of the pneumonic process. The child was discharged on the twenty-first hospital day.

A slight leucopenic effect from para-aminobenzoic acid was observed after the patient had been on the drug for nine days; the white blood count at this time was 4,700 with 57 per cent polymorphonuclears. The cephalin flocculation test was 4+ on the sixth hospital day and 3+ shortly before discharge.

CASE 7.—C. L., a 26-year-old white male (husband of patient in Case 8), was also admitted to Alexandria Hospital on July 20, 1946, with the complaints of fever of two days' duration and rash of one day's duration.

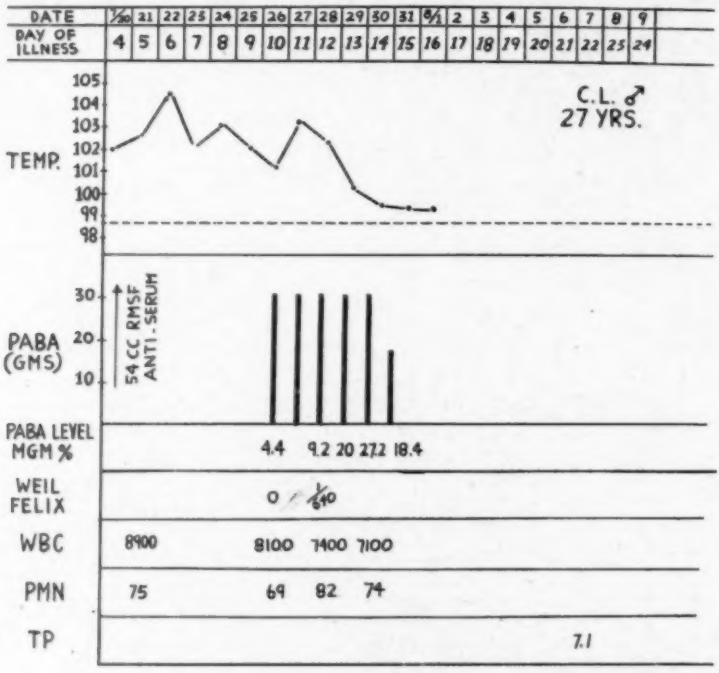


CHART 7

As in the case of his wife, the patient removed a deeply embedded tick from his right shoulder one week before admission. Five days later, a fever was noted, accompanied by malaise, chilly sensations, weakness, and muscle aches. On the day prior to entry, a faint pink rash which had its initial distribution on the hands, wrists, and ankles was observed.

Physical examination revealed a well-developed male who appeared moderately ill. There was a maculopapular rash present over the entire body but chiefly concentrated about the upper and lower extremities. Both plantar and palmar surfaces were involved. Temperature was 102° F., pulse 98, respirations 24, and blood pressure 118/80.

Laboratory examination revealed a hemoglobin of 13.5 Gm. with 4.6 million red cells; the white cell count was 8,900 with 75 per cent neutrophiles, and 25 per cent lymphocytes. The urinalysis was negative. A positive Rocky Mountain spotted fever complement fixation in a dilution of 1:512 was obtained on the sixteenth day after the onset of illness.

On the day of admission, the patient was given 64 c.c. of tick fever antiserum. Transient subjective improvement was observed during the next three days, although the temperature

continued to range between 100° to 104° F. On the fourth day, the patient appeared definitely worse with a marked increase in the hemorrhagic character of the rash and an exacerbation of malaise, drowsiness, muscle aches. On the sixth day, para-aminobenzoic acid therapy was started with an initial dose of 6 Gm. and 4 Gm. every three hours thereafter (Chart 7). Therapy was maintained for five days, during which time the patient received a total of 162 Gm. Daily para-aminobenzoic acid determinations revealed the blood level to range between 4.4 to 30 mg. per cent.

Following initiation of therapy the patient's improvement was gradual but progressive. The temperature came down to normal by lysis within four days and the rash had faded by the sixth day. The patient was discharged on the twelfth hospital day after an uneventful convalescence. No leucopenia resulting from para-aminobenzoic acid was observed.

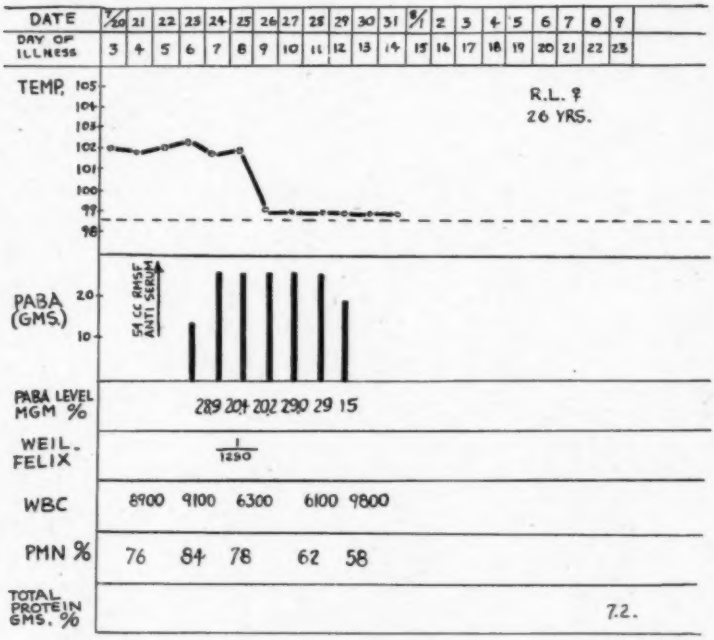


CHART 8

CASE 8.—R. L., a 26-year-old white female, was admitted to Alexandria Hospital on July 20, 1946, with the complaints of fever of two days' duration and a rash of one day's duration.

About eight days prior to entry, the patient found a tick on the back of her neck and removed it without difficulty. Five days later she began to experience some malaise and felt nauseated. On the following day an elevation of temperature was noted and the patient began to complain of muscular aches and pains. On the day before admission, a rash was noted on the hands, feet, and abdomen.

Physical examination revealed a moderately ill female in no apparent distress. There was a diffuse maculopapular rash distributed over the entire body with maximum concentration along both forearms. The pupils reacted sluggishly to light and accommodation and nystagmus

was noted on right lateral gaze; the patient complained of diplopia. Physical examination was otherwise not remarkable. Temperature was 101.6° F., pulse 110, respirations 24, and blood pressure 102/70.

Laboratory examination revealed a hemoglobin of 10.4 Gm. with 3.8 million red cells; the white cell count was 8,900 with 76 per cent neutrophiles, 22 per cent lymphocytes, 1 per cent eosinophiles, and 1 per cent monocytes. The urinalysis was negative as was the blood Kahn and Eagle. Weil-Felix agglutination test with Proteus OX19 was positive in a dilution to 1:1,280.

On the day of admission, the patient received 54 c.c. of Rocky Mountain spotted fever antiserum. However, no perceptible improvement was noted following its use; the patient continued to complain of severe headache, malaise, and diplopia and the temperature continued to spike between 100° to 102° F. On the fourth day after entry, para-aminobenzoic acid was started. The dose was 6 Gm. initially and 3 Gm. every three hours thereafter; the drug was maintained for the next six days, during which time the patient received a total of 132 Gm. of para-aminobenzoic acid. Frequent blood level determinations ranged between 15 and 29 mg. per cent (Chart 8).

Within three days after initiation of para-aminobenzoic acid therapy, a definite improvement was observed. The patient's anorexia and subjective discomfort had lessened to a considerable extent. On the third day, the temperature came down to normal and she remained afebrile during the remainder of her hospital stay. The rash had completely faded within the seventh day after para-aminobenzoic acid therapy was started. The patient was discharged on the twelfth day after an uneventful convalescence. No leucopenia from the drug was observed.

COMMENT

Our results with para-aminobenzoic acid in Rocky Mountain spotted fever were in effect similar to those obtained by Yeomans,[7] Tierney,[8] and Smith[9] against louse-borne typhus, scrub typhus, and murine typhus, respectively (Table II). The improvement was more gradual than dramatic and the temperature came down by lysis over the course of several days with concomitant improvement clinically. The morbidity, duration of the disease, and degree of toxicity seemed to be modified to a greater or lesser extent in six of the eight patients treated with para-aminobenzoic acid as compared with the thirty untreated patients observed during the previous fifteen years in Children's Hospital (Chart 9). The mortality rate among the untreated group was 10 per cent (three deaths in thirty patients) while in the eight cases managed with para-aminobenzoic acid there were no deaths. Admittedly, the latter series is too small to permit any significant statistical evaluation and only further extensive clinical trials will allow any definite conclusions regarding the efficacy of para-aminobenzoic acid in Rocky Mountain spotted fever. The evidence thus far is suggestive but not conclusive. The response to para-aminobenzoic acid was in no way comparable with the dramatic response of susceptible bacterial infections to sulfonamides and antibiotic drugs. Had therapy been started earlier in these cases, it is possible that a more prompt response might have been observed.

Mode of Action of Para-Aminobenzoic Acid.—The important role assumed by para-aminobenzoic acid in the metabolism of bacteria which multiply outside the cells of the body has been clarified since the advent of sulfonamide drugs; the antagonism between the latter and para-aminobenzoic acid is now well

known. However, rickettsias reside and multiply intracellularly, largely within the endothelial cells of small blood vessels. Para-aminobenzoic acid theoretically must gain access to the organisms located within the cell and, in a manner which is as yet strictly speculative, inhibit the intracellular multiplication of the rickettsia, possibly by virtue of stimulation of the metabolism of the host cells.

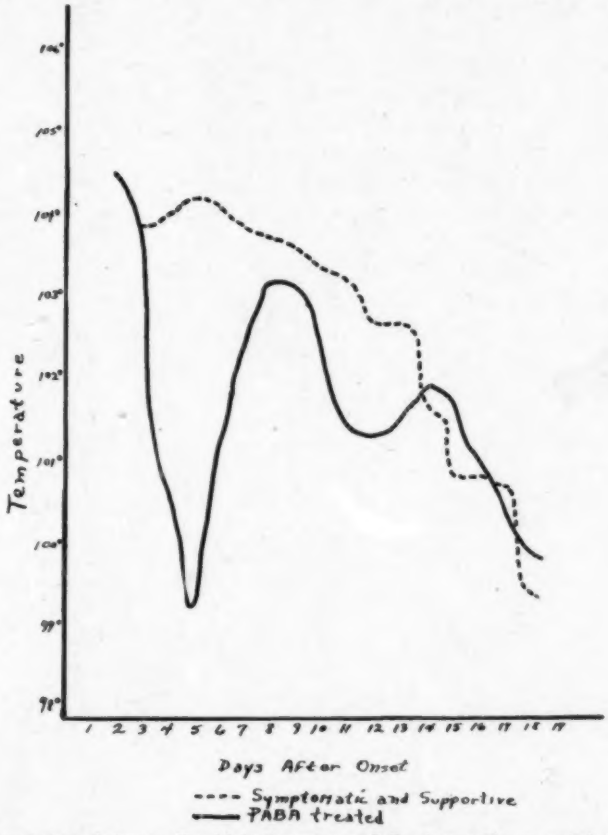


Chart 9.—Comparison between the highest average daily temperatures noted in the eight PABA-treated patients and thirty untreated patients with Rocky Mountain spotted fever.

Grieff and associates[14] hypothesize that either the high metabolic activity of para-aminobenzoic acid on the enzyme system produces an unfavorable milieu for the multiplication of rickettsia within the cell or that enzymes necessary for the growth of rickettsia disappear from the host cells. This would be in keeping with a rickettsiostatic rather than a rickettsiacidal mode of action. That para-aminobenzoic acid does not act directly on the multiplication of rickettsia is inferred from an experiment in which the organisms were exposed to a concentration of 50 mg. per cent of para-aminobenzoic acid without affecting their virulence for animals.[11] Anigstein and Bader[13] have demonstrated that pathological

lesions typical of spotted fever including a large friable spleen and pneumonitis developed in infected guinea pigs even though para-aminobenzoic acid had been administered; they further demonstrated that when the spleen from such animals was injected into susceptible guinea pigs, there resulted a fatal spotted fever infection. In the opinion of these authors the conclusion seemed warranted that para-aminobenzoic acid produces its effect by suppressive rather than destructive action on rickettsiae.

Time of Initiation of Para-Aminobenzoic Acid as Related to the Response to Therapy.—It is generally agreed that the earlier para-aminobenzoic acid therapy is initiated, the better the rickettsiostatic response. In guinea pigs experimentally inoculated with a highly virulent strain of Rocky Mountain spotted fever, Anigstein and Bader[13] found that a progressive delay in initiating para-aminobenzoic acid therapy diminished the efficacy of the drug; these authors considered a forty-eight-hour delay as probably being borderline. Yeomans and associates[7] reported that the best results in louse-borne typhus in human beings were obtained when the drug was started on the second and third days of illness, but observed some effect when the treatment was begun as late as the seventh day. Two-thirds of the cases of tsutsugamushi disease treated by Tierney[8] received the drug not later than the fifth day and no case was started on therapy later than the seventh day of illness. In both of these well-controlled series conducted under the aegis of the American Typhus Fever Commission, patients were hospitalized early and para-aminobenzoic acid therapy was begun shortly thereafter. However, early hospitalization (i.e., within two to three days after onset of fever) is not the rule in sporadic cases of tick fever in civilian practice. Only three of the eight para-aminobenzoic acid treated patients in this series were hospitalized prior to the fourth day, while the other five patients were admitted within the seventh to the tenth day after the onset of illness. Of these, only one patient (Case 3) was started on therapy prior to the sixth day. Any attempt to evaluate the time of initiation of therapy related to the duration of the disease as judged by our results would necessarily be invalid because of the small number of cases in our series. Unquestionably, Case 3, who was started on therapy two days after the onset of the disease, showed the most striking response, with the temperature returning to normal within two days after the initiation of para-aminobenzoic acid therapy. In five other cases where para-aminobenzoic acid therapy was begun within six to ten days after the onset of the disease, the response to therapy was encouraging but not remarkable, with the temperature coming down to normal within an average of six days after initiation of the drug. In the remaining two patients (Cases 5 and 6) both of whom began to receive para-aminobenzoic acid eight days after the onset of the disease, any accurate evaluation of the efficacy of para-aminobenzoic acid therapy was difficult. Both of these patients represented severe examples of tick fever and followed strikingly parallel courses. In Case 5, the drug was discontinued prematurely on the fourth day and a progressive change for the worse in the child's condition occurred, either by coincidence or otherwise, shortly therafter; the picture was further complicated by a superimposed parotitis and bronchopneu-

monia. Similarly, Case 6 was complicated by bronchopneumonia and parotitis (due to mumps) as well as mumps meningoencephalitis. These superimposed infections serve to vitiate any attempt to appraise the effect of para-aminobenzoic acid in both cases. It is worth noting that both children were delirious and comatose at a time when the para-aminobenzoic acid blood levels ranged between 40 and 80 mg. per cent. At the time, it was considered that the marked lethargy and disorientation noted in both children could have been due to any one of three causes, viz., that due to severe tick fever per se, that due to the toxic effects of the drug and third (in Case 6) that ascribable to the complicating mumps meningoencephalitis. As will be discussed later, the studies on ingestion of large doses of para-aminobenzoic acid in a series of six normal children who served as controls would make it appear that the drug was a less likely contributing factor.

As Yeomans and associates[7] have stated, it is apparent that a much wider clinical trial with para-aminobenzoic acid in rickettsial diseases would be required before it would be possible to determine the limits within which salutary effects with the drug may be expected.

Toxicity of Para-Aminobenzoic Acid.—A definite leucopenia and granulocytopenia was found in only one of the eight patients treated with para-aminobenzoic acid. In this patient (Case 1) the white cell count went down to 3,600 with 16 per cent polymorphcnuclears on the ninth day of therapy and rose within four to five days following discontinuation of drug therapy. In one other instance (Case 6) a white cell count of 4,700 with 57 per cent polymorphonuclears was noted. No definite correlation was observed between the degree of leucopenia and the para-aminobenzoic acid blood level. It is generally agreed[7-9] that if a leucopenia under 3,000 is observed, it is advisable to discontinue para-aminobenzoic acid therapy. The importance of performing daily white blood cell counts while the drug is being administered is apparent. No change was observed in the red cell count and hemoglobin.

There is no evidence thus far that para-aminobenzoic acid produces any kidney complications in a fashion similar to sulfonamide drugs which, in their chemical configuration, are related to para-aminobenzoic acid. A good urinary output was initiated in all the para-aminobenzoic acid treated cases, to forestall the possibility of producing excessively high blood levels.

In five of the six cases of spotted fever where para-aminobenzoic acid was employed, cephalin flocculation tests were obtained within twelve to nineteen days after the onset of the disease (or within five to twelve days after therapy was initiated) and in all five cases a positive cephalin flocculation ranging between 3 and 4+ were noted. In view of the fact that tick fever per se is capable of producing a pronounced reduction in liver function, there was some question whether the evidence of liver damage presented in these cases represented a dysfunction due to the disease or para-aminobenzoic acid, or both.

In an attempt to evaluate this point, a series of six controls selected at random from the wards, ranging in age between 3 and 11 years, were given 0.33 Gm. of para-aminobenzoic acid per pound of body weight in twenty-four hours

in a three-hour divided dosage schedule for four consecutive days and daily cephalin flocculation tests were obtained. In two instances the cephalin flocculation rose from 0 to 3 and 4+ within twenty-four to forty-eight hours after the initiation of para-aminobenzoic acid. In the other two cases the cephalin flocculation increased from a control 2+ to 4+ within the same interval (Table I).

TABLE I. CONTROL GROUP RECEIVING PABA*

DAYS AFTER PABA STARTED	MG. % PABA	PLATELETS	PROTHROMBIN (% NORMALCY)	CEPHALIN FLOCCULATION†	CARBON-DIOXIDE COMBINING POWER
1	15	319,000	109	0 to 4+	
2	26	352,000	103	3+ to 4+	
3	32	347,000	99	3+ to 4+	
4	37	240,000	77	3+ to 4+	36
		PABA discontinued			
6					45

*Summary of a control group of six normal children selected at random from the ward who received 0.33 Gm. of PABA per pound of body weight per twenty-four hours in a three-hour divided dosage schedule for four consecutive days. PABA levels, platelet counts, and prothrombin determinations were obtained daily on each of the six children while the cephalin flocculation tests were obtained daily on four. The carbon-dioxide combining power was done only on the fourth and sixth day of the experiment. The average of the six daily determinations in each category are noted above.

†Cephalin flocculation tests obtained prior to the administration of PABA were negative in two cases and 2+ in two others.

In a similar group of six controls receiving the same dose of para-aminobenzoic acid, daily prothrombin time determinations were obtained. It was found that the prothrombin level dropped gradually from an initial average of 109 per cent to 77 per cent of normalcy within four days. The results obtained in this control group are suggestive but by no means conclusive that para-aminobenzoic acid may exert some untoward effect on liver function. Further control studies, however, would be indicated before any categorical statement could be made. It might be well to add that in view of the fact that para-aminobenzoic acid is largely conjugated with glycine by the liver to produce para-aminohippuric acid, the possible dangers of administering the drug in the presence of a liver already damaged by spotted fever also requires further clarification.

In this regard platelet counts performed daily in the control group showed no significant reduction during the four-day period that para-aminobenzoic acid was administered.

Carbon-dioxide combining powers were also obtained in each of six cases in this control series on the fourth day of drug ingestion (Table I). Levels ranging from 28 to 44 volumes per cent with an average of 36 volumes per cent were noted. No acidotic dyspnea was noted. Two days after discontinuing para-aminobenzoic acid administration the carbon-dioxide combining power rose in all cases but one to levels ranging between 40 and 52 volumes per cent. This reduction in carbon-dioxide combining power ensued in spite of preliminary neutralization with five per cent sodium bicarbonate which was designed to lessen gastric irritation. Although this control series is small, it would seem that para-aminobenzoic acid is capable of producing a moderate transient re-

duction of carbon-dioxide combining power and it is suggested that carbon-dioxide combining power determinations be obtained periodically when the drug is employed to avoid any complicating acidosis. The mechanism of this imposed disturbance in acid-base balance is not clear.

In spite of the relatively high drug levels (up to 54 mg. per cent) attained in this control group, no evidence of drowsiness or lethargy was observed. This serves to suggest that the apathy and disorientation noted in some of the para-aminobenzoic acid treated patients (especially cases 5 and 6) may have been due to the disease rather than the drug. It should be borne in mind, however, that in the face of the evidence noted here, that para-aminobenzoic acid is capable of producing a reduction of the carbon-dioxide combining power there is the possibility that drowsiness and even coma *can* result from para-aminobenzoic acid if severe acidosis supervenes.

Optimal Dose.—The optimal dose of para-aminobenzoic acid requires further experimental and clinical experience. The drug is excreted rapidly in the urine so that at the end of two to three hours only minimal amounts are still detectable in the blood. Hence frequent administration of the drug, preferably on a two-hour dosage schedule, is indicated. Yeomans and associates[7] administered 24 to 28 Gm. of para-aminobenzoic acid orally per day (usually 2 Gm. every two hours) to adults with louse-borne typhus and considered 10-20 mg. per cent to be an adequate blood concentration. Smith[9] used a similar dosage schedule in the management of twenty-nine patients with murine typhus. In Tierney's[8] series of tsutsugamushi disease, para-aminobenzoic acid was administered in dosage of 8 Gm. initially and then 3 Gm. every two hours; on this regimen, blood concentrations of 30 to 60 mg. per cent were achieved within two days and in some cases a blood level ranging between 95 and 150 mg. per cent was attained. Tierney[8] cites one case where an acutely ill patient had two convulsive seizures at a time when he had a para-aminobenzoic acid blood level of 103 mg. per cent; however, these convulsions were thought to have been due to the disease rather than to the drug. There is no definite evidence thus far that such inordinately high doses are necessarily more efficacious than lower doses in Rocky Mountain spotted fever, and until more is known regarding the possible untoward reactions of para-aminobenzoic acid, it is probably the better part of discretion to attempt to maintain a blood level between 20 and 40 mg. per cent. In our series of six cases of tick fever in children ranging in weights from 20 to 80 lbs. we found that 0.33 to 0.5 Gm. per pound of body weight per twenty-four hours in a two-hour divided dosage schedule would usually yield a para-aminobenzoic acid blood level ranging between 15 and 40 mg. per cent. This was confirmed in a control series of six normal children (see Table I). It is well to add that in the control series, a hiatus of twenty-four to forty-eight hours was required to attain the higher levels ranging between 25 and 40 mg. per cent, suggesting that a cumulative process was operative. In agreement with Tierney,[8] we found a considerable variation from patient to patient in blood levels attained with comparable doses. The desirability of performing daily blood levels during therapy is apparent. In our cases, the para-aminobenzoic acid blood levels were routinely obtained one hour after the previously administered dose

TABLE II. SUMMARY OF 8 PATIENTS WITH ROCKY MOUNTAIN SPOTTED FEVER TREATED WITH PARA-AMINOBENZOIC ACID

CASE	AGE (YR.)	WEIGHT (LB.)	DAY OF DISEASE PABA STARTED	DAYS OF FEVER AFTER PBA STARTED	DURATION OF PABA ℞ (DAYS)	MAXIM. PBA LEVEL (MG. %)	TOTAL PABA (GM.)	LOWEST WBC	CEPHALIN FLOCCULATION	PROTHROMBIN TIME (%)	LOWEST TOTAL PROTEIN (GM. %)	MAXIM. PROTEUS OX19	SEVERITY OF CASE	OUTCOME
1. (D.B.)	4	37	9	6	10	24	108	3,600	4+	50	—	1/640	2+	Recovery
2. (S.H.)	7	45	9	5	10	37	202	6,100	—	—	5.8	1/2,560	2+	Recovery
3. (D.V.)	1½	19	2	2	8	40	74	5,700	3+	70	6.5	1/640	1+	Recovery
4. (S.W.)	8	50	10	12	9	35	186	9,500	4+	—	5.7	1/5,120	3+	Recovery
5. (J.M.)	4	31	8	22	4	80	36	8,500	4+	—	4.7	1/2,560	4+	Recovery
6. (C.C.)	11	82	8	11	9	40	104	4,700	4+	—	3.9	1/2,560	4+	Recovery
7. (C.L.)	26	150	10	4	6	27	162	7,100	—	—	7.1	1/640	3+	Recovery
8. (R.L.)	26	130	6	3	7	29	132	6,100	—	—	7.2	1/1,280	2+	Recovery

of the drug; this permitted a more uniform evaluation of the level in view of the rapid excretion of para-aminobenzoic acid within two to three hours after administration.

The optimal duration of therapy again is arbitrary pending further clinical trials. In our series, therapy was maintained for an average of seven days and was usually discontinued within two to four days after the temperature returned to normal.

CONCLUSIONS

1. A review of thirty-eight patients with Rocky Mountain spotted fever (thirty-six of which were seen at Children's Hospital), from 1931 to 1946, is presented.

2. In the eight patients with tick fever treated with para-aminobenzoic acid during the summer of 1946 (six children and two adults) it would appear that the degree of toxicity, duration of the disease, and morbidity were favorably modified to some extent when compared with the thirty untreated patients observed during previous years. The mortality rate in the untreated group was 10 per cent while there were no deaths in the eight patients managed with para-aminobenzoic acid. The latter series is too small, however, to permit any definite conclusions.

3. Administration of 0.33 Gm. of para-aminobenzoic acid per pound of body weight in twenty-four hours in a three-hour divided dosage schedule over a period of four days to six normal children in a preliminary control experiment suggested the following conclusions:

a. Para-aminobenzoic acid blood levels ranging between 15 and 36 per cent could be maintained with this dose.

b. Daily prothrombin time determinations and cephalin flocculation tests showed changes suggestive of transient liver dysfunction.

c. The carbon-dioxide combining power was also moderately reduced temporarily by the drug.

We wish to express our sincere appreciation to Dr. E. Clarence Rice for his invaluable assistance with the laboratory procedures.

REFERENCES

1. Badger, L. F., Dyer, R. E., and Rumreich, A.: Pub. Health Rep. U. S. P. H. Service **46**: 463, 1931.
2. Cecil's Textbook of Medicine, ed. 5, Philadelphia, 1942, W. B. Saunders Company.
3. Topping, N. H.: M. Clin. North America **27**: 722, 1943.
4. Harrell, G. T., Venning, W., and Wolff, W. A.: J. A. M. A. **126**: 929, 1944.
5. Snyder, J. C., Maier, J., and Anderson, C. R: Report to the Division of Medical Sciences National Research Council, Dec. 26, 1942.
6. Hamilton, H. L., Plotz, H., and Smadel, J. E.: Proc. Soc. Exper. Biol. & Med. **58**: 255, 1945.
7. Yeomans, A., Snyder, J. C., Murray, E. S., Zarafonetis, C. I. D., and Ecke, R. S.: J. A. M. A. **126**: 349, 1944.
8. Tierney, N. A.: J. A. M. A. **131**: 280, 1946.
9. Smith, P. K.: J. A. M. A. **131**: 1114, 1946.
10. Anigstein, L., and Bader, M. N.: Science **101**: 591, 1945.
11. Hamilton, H. L.: Proc. Soc. Exper. Biol. & Med. **59**: 220, 1945.
12. Rose, H. M., Duane, R. B., and Fischel, E. E.: J. A. M. A. **129**: 1160, 1945.
13. Anigstein, L., and Bader, M. N.: Texas Rep. Biol. & Med. **4**: 260, 1946.
14. Grieff, D., Pinkerton, H., and Moragues, V.: J. Exper. Med. **80**: 561, 1944.
15. Snyder, J. C., cited by Yeomans et al.[7]

THE EFFECT OF TRIMETHYLOXAZOLIDINE DIONE (TRIDIONE) ON THE BLOOD

JEAN P. DAVIS, M.D., AND WILLIAM G. LENNOX, M.D.
BOSTON, MASS.

RECENTLY we have reported the clinical results of administering Tridione to 245 patients of various ages.[1] We also reported promising results with the homologue of this drug, dimethylethyloxazolidine dione, in eleven patients not completely relieved of petit mal by tridione. The beneficial effects of these drugs on the petit mal triad of epileptic seizures are most encouraging.

Because of disturbing reports of reactions in the blood following the use of tridione, including two deaths from aplastic anemia,[2, 3] in the past six months we have examined the blood of all patients taking tridione under our supervision, at monthly intervals. The present report deals with 127 patients and 327 individual examinations. These have been made with the cooperation of the department of clinical pathology at the Children's Hospital in Boston, or by the patient's physician. The examinations have included a total white blood cell count and differential, observation of the adequacy of platelets, and determination of the hemoglobin. The latter has been made by the acid-hematin method, usually with the Haden-Hausser or Sahli-Hellige hemoglobinometer.[4] Red cells were counted when the hemoglobin was considered low. In twenty of these patients, constituting a small control series, counts were made before medication was started. Comparisons have been made only with the average values for this premedication group. The number of counts obtained is considered too small, and the range of error too great for analysis of these figures in greater detail.

The ages of the patients range from 8 months to 50 years. Distribution of ages are: less than 2 years of age, 3 per cent; 2 to 4 years, 6 per cent; 4 to 8 years, 23 per cent; 8 to 12 years, 21 per cent; and above 12 years of age, 46 per cent. 65 per cent fall between the ages of 4 and 16 years. Because less than 10 per cent of patients are under 4 years of age, the findings in the entire group are compared with the standards used for adults.[5]

A comparison of the average blood findings in patients (before and during tridione medication) and in normal adults is shown in Fig. 1. Although patients both before and during medication have had low hemoglobin values, the difference between the two groups is not significant. Only 3 per cent of patients taking tridione have had values below 11 Gm., none has been below 9.9 Gm., and none has evidenced an abrupt fall, even among those who have experienced leucopenia.

There has been no decline in the platelet count of any of the patients, and none of the series has observed increasing bleeding or bruising tendencies while taking tridione.

From the Department of Neurology, Harvard Medical School and the Children's and Infants' Hosptial of Boston, number L in a series, "Studies in Epilepsy."

The most pronounced changes, as one would expect, have been in the number and proportion of leucocytes. The average number of leucocytes for the entire group of treated patients is 8,300 per cubic millimeter, of which 50 per cent are neutrophiles. This figure is well within the normal range, but slightly lower than that for the premedication group. The cumulative frequency distribution curve of the total white blood counts for this series (Fig. 2) shows a striking parallelism to the range of normal values as compiled from various series of comparable random counts which are reported in the literature.[6]

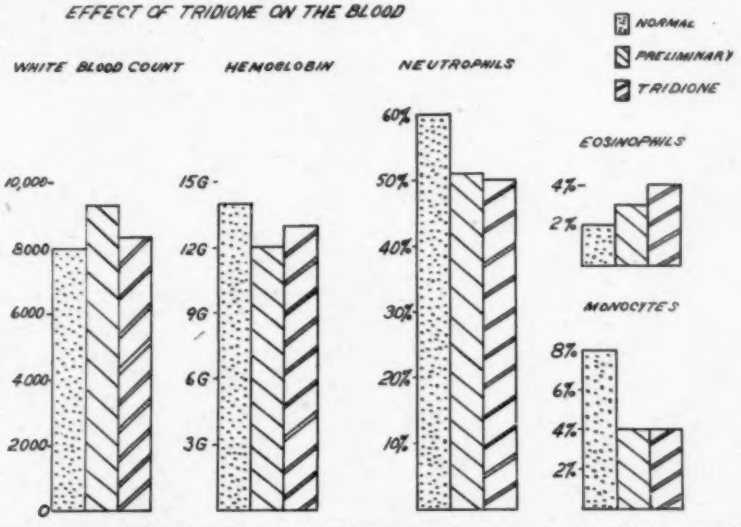


Fig. 1.—The effect of tridione on the blood. The three columns at the left represent the average number of leucocytes in three groups, namely, the literature normals (dotted column), preliminary examination of twenty patients (single cross-hatched), and 127 patients taking tridione (double cross-hatched). The second triplet of columns represents the hemoglobin in grams in these three groups. The third group of columns represents the proportion of leucocytes which was neutrophiles. The right end group of columns represents the proportion of eosinophiles and of monocytes in these three groups.

Because the drug in question acts primarily on the granulocytes (neutrophiles or polymorphonuclear cells) produced in the bone marrow, the absolute number of neutrophiles is probably of more significance than either the total leucocyte count or the proportion of neutrophiles to the total.

A spot chart (Fig. 3) comparing the number of neutrophiles with the total leucocyte count demonstrates the relationship between these two values for each of the individual determinations made, before tridione therapy was started and during the course of treatment; the latter include both the group which maintained a satisfactory level of neutrophiles and the 17 patients whose counts were classified as borderline or neutropenic. The 50 per cent average for the patients receiving tridione is definitely lower than the normal average, usually quoted to be approximately 60 per cent. All of the patients with neutropenia or borderline counts fall on or below the 50 per cent diagonal.

The distribution of the total number of neutrophiles per cubic millimeter for the group (Fig. 4) of 127 patients studied is as follows: eight, or 6.3 per cent, have had a definite leucopenia with a total number of neutrophiles below 1,600 per cubic millimeter. The average number per cubic millimeter for this group is 1,265; the lowest is 600. This last value is in a 5-year-old boy who had taken tridione continuously for nine months. An additional nine patients,

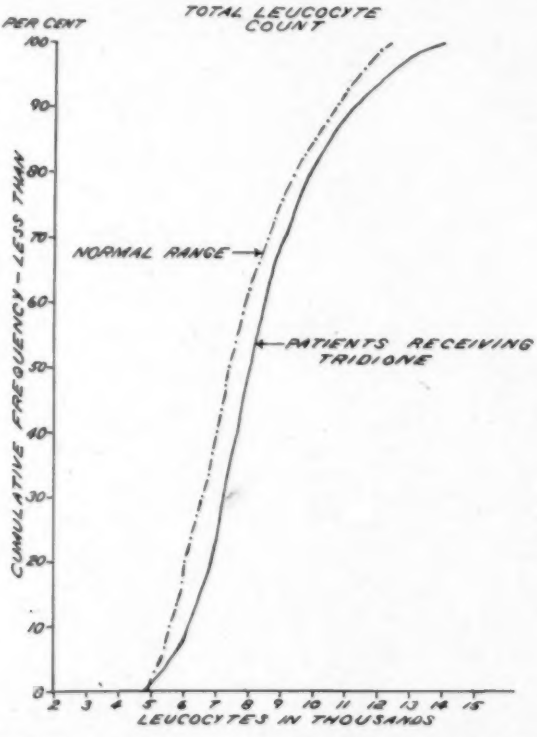


Fig. 2.—Comparison of cumulative frequency distribution curves for the total leucocyte counts of the patients receiving tridione with the average normal range from the literature. Each point on the curve represents the total percentage of counts on the ordinate scale, for which the total number of leucocytes is less than the corresponding value represented on the abscissa.

or 7 per cent, have had borderline values ranging from 1,600 to 2,500 neutrophiles, per cubic millimeter. Thus, a total of 13.3 per cent of patients have had an abnormally low number of neutrophiles, less than 2,500 per cubic millimeter. A further 7 per cent have had counts which might be considered as low normal, ranging from 2,500 to 3,000.

Of the eight patients whose neutrophiles have numbered less than 1,600 per cubic millimeter, two have continued to take tridione, and subsequent values have remained above 2,700 per cubic millimeter. In a third, medication has

been gradually resumed to a full dosage over a period of eight weeks, without recurrence of the neutropenia. Medication has been discontinued in the other five patients with prompt and satisfactory return to a normal number of granulocytes. None of these eight patients has displayed any distinct alteration of the morphology of the neutrophiles.

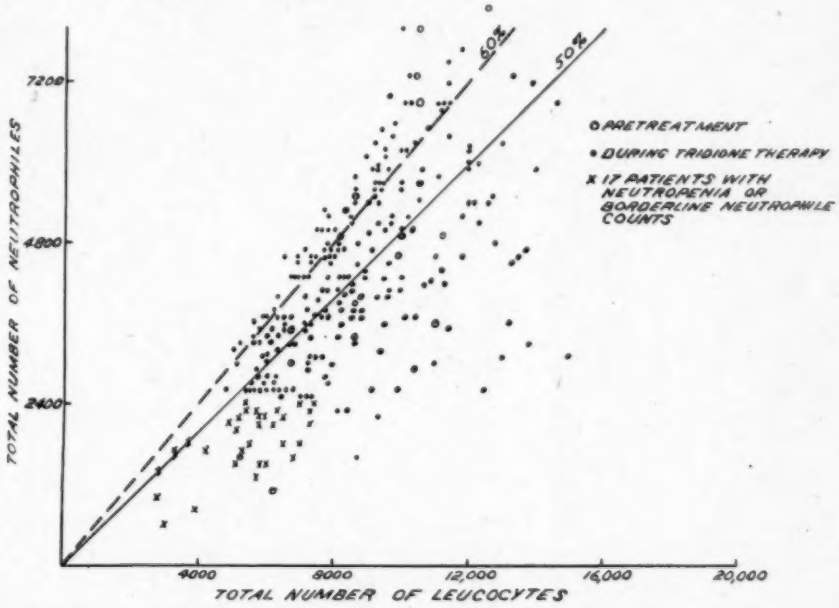


Fig. 3.—A spot chart comparing the total number of leucocytes with the total number of neutrophiles for each individual leucocyte count. The circles represent the values for the pretreatment counts, the dots, the figures for patients receiving tridione, and the crosses, the figures for the seventeen patients with neutropenia, or borderline counts. The scattered dots to the right represent the counts made on the few infants included in the study. The solid line represents the 50 per cent average determined for all counts made on the patients receiving tridione, the interrupted line, the 60 per cent, or normal literature average.

No correlation has been discovered between the occurrence of neutropenia and the age or sex of patients, the dosage of tridione, or interruptions of treatment. Of the 17 patients with neutropenia, 15 per cent had a rash previous to, or coincident with the leucopenia, compared with 37 per cent of the whole series of 127 patients. None of the patients with neutropenia has experienced any clinical symptoms referable to the lowered neutrophile count.

The neutropenia in these eight patients developed from three weeks to twenty months after the institution of tridione therapy, the average being 9.4 months. Five of the eight patients with neutrophiles numbering less than 1,600 per cubic millimeter, and seven of the nine with borderline counts of from 1,600 to 2,500, had blood examinations one month prior to the onset of definite neutropenia. At that time, six of these twelve patients had evidence of a declining neutrophile count.

Cumulative frequency distribution curves of the percentage of the various types of leucocytes in the group studied are compared in Fig. 5 with normal values for the range of leucocyte variations reported in the literature.[7] The average percentage of neutrophiles for the 327 examinations in the entire series of 127 patients is 50 per cent; 36 per cent of the patients have had average counts below this level, and in 12 per cent the average values are below 40 per cent. The values between the fiftieth and ninety-fifth percentile levels are almost identical in the two groups.

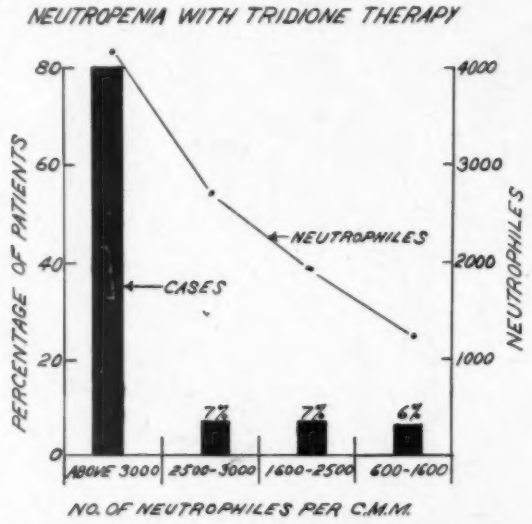


Fig. 4.—Distribution of the total neutrophile counts for 127 patients receiving tridione. The solid column to the left represents the percentage of patients whose total neutrophile counts are above 3,000. The second column, the percentage of patients whose counts range between 2,500 and 3,000; the third column, the percentage of patients whose counts range from 1,600 to 2,500 (the borderline group), and the column on the right, the percentage of patients with definite neutropenia, or neutrophile counts below 1,600 (from 600 to 1,600). The broken line above represents the average number of neutrophiles for each of the four categories, recorded on the scale to the right.

The average percentage of lymphocytes in the group receiving tridione is significantly higher than the percentage considered to be the average "normal" value. The proportion of lymphocytes is 40 per cent or over in 55 per cent of the patients, compared with a proportion of about 13 per cent of "normal" persons. The proportion of lymphocytes is less than 30 per cent in 31 per cent of "normal" persons, and in only eight per cent of patients taking tridione. The fiftieth and ninety-fifth percentile values for the patients are approximately 41 and 60 per cent lymphocytes respectively, compared with about 33 and 44 per cent for the average "normal" range.

Our results, which demonstrate the failure of tridione to alter the total leucocyte count in spite of a decline in the number of circulating neutrophiles, indicate that there may be an absolute increase in the number of lymphocytes. The data suggest that tridione may have a mild but significant stimulatory effect on the lymphocytic series.

The proportion of monocytes in normal persons is believed to be from 5 to 12 per cent. In our patients the proportion is from zero to 12 per cent. In the majority of patients counts tended to be unusually low. Thus, considering

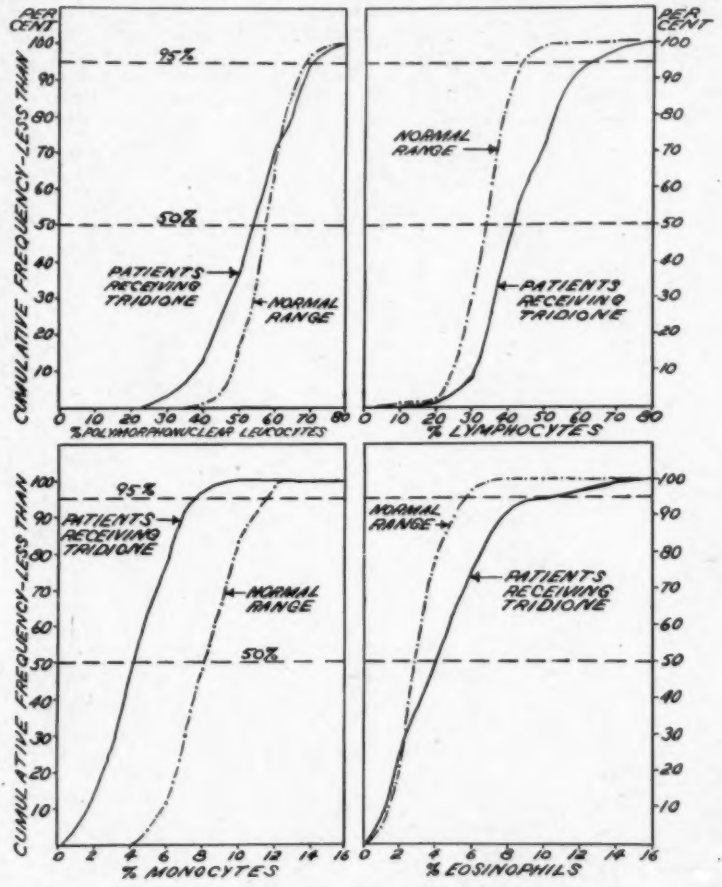


Fig. 5.—Cumulative frequency distribution curves comparing the percentage of polymorphonuclear leucocytes, lymphocytes, monocytes, and eosinophiles of patients receiving tridione with normal values compiled from the literature. The curves are plotted in the same manner as those in Fig. 2.

persons falling in the 50 percentile portion of the curve, the proportion of monocytes is less than 4 per cent in patients taking tridione, and approximately 8 per cent in the "normal" population. Among those in the 95 percentile group, monocytes form less than 8 per cent of leucocytes in the treated group and less than 11 per cent in the "normal" group.

An eosinophilia of 5 per cent or more has occurred at some time in 52 per cent of the treated patients, the maximum being 25 per cent. One-half

the total group have had average values of 3 per cent or below, and one-fourth average values above 6 per cent. Tridione was withheld from nine of the patients whose eosinophilia was 10 per cent or higher (Table I). The eosinophiles averaged 14.8 per cent in this group, and at the time of withdrawal the patients had been taking tridione from five weeks to two years. Because in some of the patients eosinophilia was present at the first examination, the onset of eosinophilia, in relation to the duration of therapy is not known. In eight of the nine patients, from two to six weeks after omission of tridione, the proportion of eosinophiles fell to an average of 6.9 per cent. Therapy was resumed in seven of these patients, and the percentage of eosinophiles rose again to an average of 9.7 per cent in from one to eight weeks. In two of these patients, however, the proportion of eosinophiles did not increase.

TABLE I. STUDY OF EOSINOPHILIA IN NINE PATIENTS RECEIVING TRIDIONE, AND THE EFFECTS OF WITHDRAWAL AND RESUMPTION OF MEDICATION

	EOSINOPHILIA WITH TRIDIONE		PERCENTAGE EOSINOPHILES AFTER WITHDRAWAL OF TRIDIONE		PERCENTAGE EOSINOPHILES AFTER TRIDIONE RESUMED	
PATIENT	TOTAL NO. WEEKS OF TRIDIONE THERAPY	PERCENTAGE EOSINOPHILES	NO. WEEKS WITHOUT TRIDIONE	PERCENTAGE EOSINOPHILES	NO. WEEKS OF TRIDIONE THERAPY	PERCENTAGE EOSINOPHILES
F. D.	80	21	2	18	2	9
C. N.	36	18	4	4	2	18
J. A.	45	17	6	8	Not started again	
L. B.	78	16	2	1	Not started again	
V. F.	12	13	4	7	2	9
D. R.	36	13	2	6	4	11
N. Y.	100	13	2	1	1	4
J. C.	20	12	2	3	8	25
H. P.	5	10	1	14	4	11
Range	5-100	10-21	2-6	1-18	1-8	9-25
Average		14.8		6.9		9.7

Eosinophilia has not been confined to the group having neutropenia, although the average percentage for this group is 6.2 compared with 3.8 for the entire series. The high incidence of clinical allergy in the patients or immediate families in the whole group doubtless has some bearing on these figures and deserves further investigation.

DISCUSSION

The etiology of agranulocytosis is described by Dameshek[8] as a combination of a drug or chemical, and an allergic or sensitivity reaction toward it. Several authors have emphasized the effect of substitutions in the benzene ring,[9] presence of the benzamine nucleus, or the NH (imido) radical, whether the latter remains as NH, or whether the H is replaced by another group.[10] Opinions differ, however, concerning the relative importance of these chemical relationships. As may be seen in Fig. 6, the tridione nucleus contains a methyl group, substituted on the imido nucleus, and, in addition, a complex dione ring.

As for the influence of allergy, the patients included in this survey were questioned regarding the presence of allergic conditions personally, or among near relatives. Of 119 patients from whom reports were obtained, a personal history of major clinical allergy in the form of allergic rhinitis, asthma, eczema, or severe urticaria was obtained in 20 per cent. An additional 10 per cent complained of minor allergic conditions, such as drug rashes, mild urticaria or eczema, or gastrointestinal allergies. The immediate families of 30 per cent

TRIMETHYLOXAZOLIDINE DIONE

(TRIDIONE)

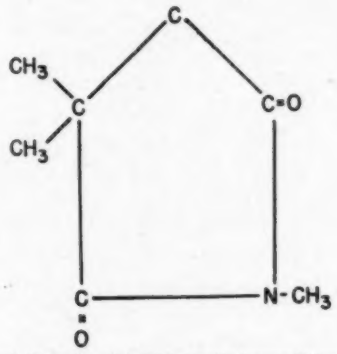


Fig. 6.—The structural formula of 3,5,5-trimethyloxazolidine-2,4-dione (tridione).

of the 119 patients had a history of major clinical allergies, and an additional 10 per cent had such a history among persons related to the patient through the preceding generation. A total of 59 per cent of these 119 patients had a positive personal or family history of allergy. The estimated incidence of allergy for the general population is about 10 per cent for frank allergies[11] and no more than 10 to 20 per cent for conditions accepted as having a truly allergic basis.[12] The incidence of allergy among our patients seems abnormally high, but we have no data, collected in a similar manner, to include both personal and family history for persons who are not epileptic. Of the patients who developed a neutropenia of 2,500 per cubic millimeter or less, and whose history of allergy was known, 62 per cent had such a personal or family history. Of the patients whose blood remained normal, 50 per cent had a positive history. This study includes such a small number of patients with neutropenia, that this incidence does not necessarily add weight to the presumed factor of allergy in the etiology of this condition. However, patients subject to seizures are possibly an unusually susceptible group. Apparently tridione has no adverse effect on the blood of animals.[13] Nonepileptic persons have not been tested. Many clinicians have argued in favor of epilepsy and migraine as allergic phenomena. Dewar[14] has reviewed the subject critically. The whole question of

any possible relationship deserves further investigation. A review of the therapeutic effects of tridione appears elsewhere.[15]

Also of interest is the absence of an immediate explosive reaction to the administration of tridione. Leucopenia in our patients developed only after weeks or months of use. The two patients, reported by others,[2, 3] who succumbed to aplastic anemia had been taking tridione for months. The blood had not been examined prior to the development of serious symptoms. This evidence of a slowly developing leucopenia allows encouragement to the use of tridione provided the blood is examined periodically. Probably, real danger does not threaten until leucopenia is followed by appreciable reduction of platelets in the blood smear.

SUMMARY

The blood of 127 patients taking tridione was examined periodically. The only significant changes were a tendency to neutropenia or eosinophilia, and a slight increase of lymphocytes. Definite neutropenia was present in 6.3 per cent of patients and borderline values in 7 per cent. In the remaining 87 per cent of patients, the number of neutrophiles remained within normal limits. Repeated examinations indicate that the neutropenia is a gradual reaction. Monthly testing would seem sufficient to prevent the development of serious neutropenia. Presumably, as with many drugs in common use, precipitate allergic reactions may occur, but we have not observed evidence of this among the patients whom we have studied.

Tridione is a potent therapeutic agent and possible effect on the blood or the bone marrow should not prevent its proper use. The following rules should be observed.

1. Tridione should be used only when specifically indicated, and under medical supervision.

2. It should not be prescribed for patients with a history of blood dyscrasia and only cautiously for those with a history of idiosynerasy to drugs.

3. The blood should be examined monthly.

4. Patients with total neutrophile counts below 2,500, should be checked more frequently, and if the neutrophile count goes below 1,600, therapy should be withheld.

ADDENDUM

We have learned of two additional deaths, as yet unreported, of patients who developed aplastic anemia after taking tridione (with other drugs) for a number of months.

REFERENCES

1. Lennox, W. G., and Davis, J. P.: The Effect of Trimethyloxazolidine dione and of Dimethylethyloxazolidine dione on Seizures and on the Blood. The Proceedings of the Association for Research in Nervous and Mental Disease, Baltimore, Williams and Wilkins Co. (In press).
2. Harrison, F. F., Johnson, R. D., and Ayer, D.: Fatal Aplastic Anemia Following Use of Tridione and a Hydantoin, J. A. M. A. 132: 12, 1946.
3. Mackay, R. P., and Gottstein, W. K.: Aplastic Anemia and Agranulocytosis Following Tridione, J. A. M. A. 132: 13, 1946.
4. Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods, ed. 10, Philadelphia, 1943, W. B. Saunders Co.

5. Wintrobe, M. M.: Clinical Hematology, 2nd ed., Philadelphia, 1946, Lea and Febiger Co.
6. Garrey, W. E., and Bryan, W. R.: Variations in White Blood Cell Counts, Physiol. Rev. 15: 597, 1935.
7. Medlar, E. M.: The Extent of Variations in the Leucocytes of Normal Individuals, Am. J. M. Sc. 177: 72, 1929.
8. Dameshek, W.: Agranulocytosis, Oxford University Press (1944).
9. Best, C. H., and Taylor, N. B.: The Physiological Basis for Medical Practice, 3rd ed., Baltimore, 1943, Williams and Wilkins Co.
10. Herz, L. F.: The Role of Amidopyrine in the Etiology of Granulocytopenia, With Special Reference to Its Chemical Structure, J. Lab. Clin. Med. 20: 33, 1934.
11. Vaughan, W. T.: Practice of Allergy, St. Louis, 1939, The C. V. Mosby Co.
12. Urbach, E., and Gottlieb, P. M.: Allergy, 2nd ed., New York, 1946., Grune and Stratton.
13. Richards, R. K., and Everett, G. M.: Tridione, A New Anticonvulsant Drug, J. Lab. Clin. Med. 31: 1330, 1946.
14. Dewar, D. C.: The Allergic Approach to Epilepsy, Practitioner, 147: 776, 1941.
15. Lennox, W. G.: Tridione in the Treatment of Epilepsy, J. A. M. A. 134: 138, 1947.

PSYCHOLOGICAL CONSIDERATIONS IN A GROUP OF CHILDREN WITH POLIOMYELITIS

EDITH MEYER, PH.D.
BOSTON, MASS.

ILLNESS can become a significant factor in the psychological development of the individual if one accepts the general notion that psychological as well as biologic development is determined by the constant interaction between the growing human organism and its environment. Illness may not only interfere with the orderly growth of the individual but also create a new medium of experiences to which the individual must adapt.

This paper will discuss certain psychological aspects of illness which in theory are becoming more widely accepted by the modern pediatrician but in practice still do not receive sufficient consideration. The psychosomatic approach stresses the intrinsic relationships of psychological and physiologic factors in human functioning. Neurologists and psychologists are aware of the disturbances in mental functioning resulting from injuries to the nervous system. The pediatrician is faced almost daily with the problems of children who, after apparent complete recovery from a serious febrile illness, still need a good deal of protection from the daily strains and who, without this precaution, are likely to present puzzling behavior problems to their parents and teachers. The pediatrician is fully aware, also, of the many psychological problems involved in the rigorous administration of any treatment plan which calls for hospitalization, immobilization, or complete bed rest for children with diseases like rheumatic fever, tuberculosis, osteomyelitis, and others. All physicians encounter, at one time or another, the psychological problems centered around the reactions of the individual to physical handicap which may be a congenital or an early acquired impairment, progressive decrease of function through illness, or sudden loss of function either through accident or illness.

A group of children with poliomyelitis provides the material for preliminary study of the various mentioned aspects. The study opens up a few avenues for future research on a variety of pediatric conditions with problems similar to those of children with poliomyelitis.

MATERIAL AND METHODS

The findings reported here result primarily from the study of a group of fifty-two patients with poliomyelitis followed from 1943 to 1946. It was started during an acute epidemic in New Haven, Conn., and continued through contacts with the children at regular intervals. The material was rounded out by observations on patients with poliomyelitis and other disorders studied in Boston. (These are being reported in other papers.)

From the Pediatric Department of Harvard Medical School and The Children's Hospital, Boston.

Aided by a grant from the National Foundation for Infantile Paralysis.

An essential part of the material which is discussed in this paper was collected at the New Haven Hospital, where the facilities of the Pediatric Department of Yale University were generously made available by Dr. Grover Powers and his staff. Their constant interest and valuable aid are gratefully acknowledged.

The children included in the main body of the study ranged from 18 months to 14 years of age, with the following distribution:

One child	18 months
5 children	2 years
7 children	3 years
5 children	4 years
6 children	5 years
5 children	6 years
6 children	7 years
3 children	8 years
8 children	9 to 12 years
6 children	12 to 14 years

These cases were, on the whole, unselected, though all children with obvious signs of retardation or any history of previous neurological disorder were excluded. They were chosen with the aim of selecting families which would be available for regular follow-up. Ten of the total were referred to the psychologist by the resident physician for attention because of questionable encephalitic involvement. Thirty-eight were chosen during the height of the epidemic while the children were still on the isolation ward. Twelve were added to the group later within the first few months of convalescence.

After the acute phase of the illness, eighteen of the children under consideration were discharged home, either as completely recovered or with minimal residual paralysis. Twenty-seven with more serious involvement were transferred to other institutions where they were to receive medical treatment for periods of time varying in length from a few weeks to years.

The various methods used to obtain psychological information were as follows: During the acute stage of the illness the children were seen regularly on the ward. No formal psychological examination was possible at this time. Informal contact, conversation, observation, and reports of the medical and nursing staff provided an initial picture of the individual child. Extensive interviews with both parents were held during the same period. They furnished information about development, personality, background, and were corroborated, wherever possible, by the information obtained by social worker and psychiatrist. At this time as well as during all the stages of the research, the close cooperation between all those who contributed to treatment or planning for the patient was considered essential for the success of the study.[1, 7]

For various reasons to be discussed later, only thirty-two were followed systematically after recovery. All of these were seen once or twice within the first year. Fifteen were seen repeatedly after this during the second and third year. Psychological examinations were given in all of these interviews and were corroborated by discussions with parents and teachers, and with social workers in the case of children in the convalescent homes. The psychological tests were the common methods used for evaluating mental ability (Gesell Developmental Schedule, Stanford-Binet, Wechsler-Bellevue, Merrill-Palmer) supplemented by a series of special tests designed to examine certain of the functions which are particularly likely to be impaired by damage to the nervous

system. Among the tests used are the various Memory-for-Design tests (Ellis, Gesell, Goldstein Stick Test), Formboard tests (Pintner-Patterson and others), Block Design Tests (Kohs, Goldstein) and various learning tests (Rey and others). Their usefulness has been discussed in medical as well as psychological literature.[6, 9, 10]

RESULTS

I. In the group of children who were *clinically fully recovered* as far as motor functions were concerned. During the first weeks after discharge from the hospital or from a short stay in one of the convalescent homes there were a great many complaints of difficult behavior.

A. In the *3- to 5-year-old group,* all of the fourteen children who were discharged as recovered were reported as having some kind of behavior problem. They were hyperactive, irritable, or disobedient, or, in some instances, too dependent or "whiney." In nine of the fourteen patients, the mothers were sure that the behavior had changed since the illness. They most frequently stated that the child had formerly been somewhat difficult "but never like this." The parents' accumulated anxieties manifested themselves in different ways, ranging from overindulgence and concern to the desire to incorporate the child as quickly as possible back into the family routine and to forget about the illness. Ten of these fourteen children were given psychological tests. They all had average intellectual abilities on the standard tests but in nine of them some jumpiness, irritability, or timidity and uneasiness were noted during the examination. Five of the children (one with frank and two with questionable encephalitic involvement) showed some difficulty in drawing, copying of forms, memory-for-design, and formboard tests. The quality of their achievement in matters involving form comprehension was below that of their achievement in other fields. In further contact with these children and their mothers, it was found that the acute difficulties disappeared gradually. Of great help here were the facilities of the so-called Curative Work Shop in New Haven, which established a special nursery school for these children. The children were given exercises, supervised play, and rest periods for a few hours of the day. This gave the children the advantage of outside experience and afforded the mothers the relief from complete care. Several of the 5-year-olds who entered school during the year after onset of the illness had some problems in reading and writing and on reexamination still presented the difficulties in form comprehension which were noted earlier.

CASE REPORTS

CASE 1.—A boy of 4 years, 10 months, was admitted to the hospital with stiffness of neck and back. Diagnosis was poliomyelitis with involvement of neck, back, arms, and intercostals. Patient was the eldest of four children with a brother of 2 years and twin sisters of 3 months. His development was normal and he was well behaved and easy to handle.

During hospital stay he was cooperative and uncomplaining while given physical examination. Later he became uncooperative and drowsy and still later was noisy and irritable.

He was discharged after a stay of three weeks without evident impairment, and was referred to orthopedic clinic for physiotherapy once a week for the next three months.

Four Weeks After Discharge.—Psychologist's notes: active, lively, highstrung little boy who talks well and has altogether average intellectual abilities. His mother finds him irritable, stubborn, and difficult. He has temper tantrums and is difficult to reason with. Mother is harassed and overworked with the care of the children and finds that the child needs more attention and patience than she can give him now.

Later.—He is living with grandmother where he is doing excellently and where he has a quiet convalescent time.

April, 1944, Seven Months Later.—Boy is doing well in curative workshop, and has quieted down considerably.

Summary.—The temporary difficulty which this child displayed after discharge from the hospital could in this case be explained by the child's still fragile emotional state after serious illness and period of hospitalization. He was unable to take his ordinary place, without concessions, in the rather lively family group.

CASE 2.—This boy of 3 years, 2 months, was admitted to the hospital with a complaint of fever, vomiting, stiff neck, and difficulty in swallowing. There was one brother of 5 years. Child's development was considered normal except for the following facts: At the age of 6 weeks he was hospitalized because mother felt that milk was giving out and wanted him taken off the breast. Baby gained steadily. At 21 months, child was a behavior problem, would not go to sleep until eleven or twelve o'clock at night, and pushed mother away when she tried to lie down beside him. He ate well. At 33 months, he had temper tantrums, threw things, and began to swear when ignored. At this time there was considerable conflict between parents over financial matters. They were referred to a psychiatrist but never followed this up. At 35 months, patient had tonsils and adenoids removed.

Behavior in the hospital was active and altogether friendly. He was discharged after three weeks on complete bed rest for two weeks. On discharge he was active but very pale.

Two Weeks After Discharge.—The mother complained about his bad temper and difficult behavior. She said that the child had changed, that he swore and threw objects.

Six Weeks After Discharge.—Psychologist's notes state the child seems intelligent and high strung, active and willful, does not follow directions too well but is essentially delightful, and full of ideas which are not always carried out but quickly abandoned. Nursery school curative workshop was advised.

Three Months Later.—He is doing well in workshop, and is considered a good member of the group, somewhat tempestuous but not difficult to handle. Mother is reported to be happier.

Summary.—It is interesting to note that in this case the mother-and-child relationship has been difficult from the very beginning. After the polio episode the mother was inclined to forget the previous problems and to blame any behavior difficulty on the illness. The convalescent child reacted violently to the mother's anxiety. The situation was relieved by pointing out to the mother that the child was essentially not changed and was able to respond satisfactorily to nursery school technique.

CASE 3.—A girl of 5 years, 9 months, was admitted with acute poliomyelitis, with some apparent encephalitic involvement. This was an only child of divorced parents. Development was normal and she was always considered bright and cheerful. She entered first grade a few days before onset of illness.

During her hospital stay she was active, friendly, and had a tendency to monopolize the attention of adults. She became irritated whenever other children received attention. She was talkative, with a quite elaborate vocabulary, and was playful and imaginative. She was discharged after three weeks as fully recovered without any paralytic involvement. Approximately four weeks after discharge she went back to school.

Six Months After Discharge.—Psychological notes: She is sociable and friendly, a child who is apparently accustomed to the affection of adults. She is rather jumpy and occasionally a little willful when encountering demands which she tries to avoid. The child appears brighter

than her I. Q. of 100 would indicate. She does well in tasks which can be solved quickly but often answers too impulsively. She has short attention spans and is quite poor in visualization. The child does badly in formboards, using empirical method rather than foresight. This adds to her many errors. When she becomes fatigued she gets overactive. Mother reports school adjustment is only fair. She gets up in class, and has difficulty in accepting school routine.

Twelve Months After Discharge.—Psychologist's notes: Child is less unstable but still very easily distractible. She continues to have difficulty in concentration and has a rather immature attitude toward outside demands. She is very dependent on adult approval. Attention spans are still short. The test results are essentially the same as those found six months earlier. She has improved in visuo-motor functions but is still poor in formboards, drawing. She is two years below her general mental level in Kohs Block Designs. Mother wonders whether child is slow. She has difficulty in arithmetic and the teacher is dissatisfied with the child's effort to pay attention in class. She has been promoted to second grade though her school achievements are not convincing. The family moved and no further contacts were available.

Summary.—Though essentially recovered, this child presented a variety of problems. She was easily fatigued and in her psychological picture showed short attention spans and some quite definite symptoms (lack of form comprehension, etc.) indicating sequelae of cortical involvement. The child's obvious tendency to be somewhat jumpy and overactive seemed accentuated by the illness.

B. The *older children* of the recovered group presented the following picture:

Five of the older children (all boys) went home and returned to school after periods ranging from one to three months. Four out of five found it hard to make up for the lost work. Though in all of these cases the teachers were said to be lenient and indulgent, the child found the work hard, got tired easily, and was unhappy in school. Three had difficulties at home, and all five were described by their mothers as being nervous and likely to cry at the least provocation. Two mothers stated that they thought their child had lost all sense of humor. Three of the children had been outstanding in sports and resented not being allowed to enter in any of these activities now. The psychological examinations of these five children four months after onset of illness showed adequate intelligence in the conventional type of test. Three of them had decided difficulty in tests requiring form comprehension, form analysis, and memory for designs; two did poorly only in memory for designs. Four out of five had difficulty in sustaining attention for prolonged periods and therefore did poorly in learning tests. Here, as in other cases in which difficulties were described, it seemed most probable that these were of recent origin. Had they been of longer standing, the child would have hardly been able to attain the level which he had reached previous to his illness and which was still evident in his stock of information and modes of thinking.

In the majority of cases, some of these difficulties of mental functioning continued for the first year and were quite evident in the psychological examination. Attention problems diminished first but comprehension of form materials still remained a source of concern for some time. Gradual improvement was noted in general, although none of the children have become particularly able in any of the mentioned functions.

CASE 4.—A boy of 11 years, 8 months, was admitted to the hospital because of nausea and stiffness of legs and was given a diagnosis of poliomyelitis. One brother 14, a sister 5 years, 6 months, and a sister of 4 months completed the family. The child's development was normal though he had been nervous, had had nightmares, and had walked and talked in his sleep. These symptoms were most prominent after arrival of his sister, but had largely disappeared. He is said to be jealous of the privileges of his older brother, and is doing well in seventh grade. He is active and alert and gets along well with everybody. He helps in a laundry and likes to do outside jobs. He is interested in sports.

During his stay in the hospital he was cooperative and friendly. He was interested in the other boys and was somewhat of a leader. He was intelligent and alert.

He was discharged after three weeks as essentially recovered. He was to have complete bed rest for two weeks and then was to be followed in the orthopedic clinic with physical therapy. This has continued for three months.

January, 1944, Three Months After Discharge.—Said to be irritable, jumpy, and was asking a great many questions about his uncle who had polio approximately twenty-four years ago and who still had "bad legs."

March, 1944, Six Months After Discharge.—In psychological interview he seemed rather tense, ambitious, and not too sure of himself. Altogether he has superior mental abilities and good consistent working habits, with a tendency to be better toward the end of a task than at the beginning. Reasoning ability is on a 14-year-old level and above; I. Q. is 120 to 125. Fails on memory-for-design tests on 11-year-old level and does relatively poorly (compared with other performances) in Kohs Block Designs and Formboard Tests. Mother reports him to be jumpy and irritable, crying easily, a thing which hardly ever occurred before illness. Resents not being allowed to enter sports or do after-school jobs.

January, 1945.—The boy has been back on full activity. He looks older than his age and works as a bootblack after school. He is doing well in the eighth grade. He wants to go to Military Academy. Psychologist's notes: Essentially the same results as noted in previous interview. Boy is still tense and rather jumpy but altogether is doing very well. Inferiority of visuo-motor functions is still present but verbal abstract abilities are excellent. The question remains as to whether these inabilities always may have been present and may have been compensated early in his mental development by his other abilities. Mother and patient are anxious to close the polio episode. No further follow-up.

Summary.—This essentially able and well-adjusted boy had shown signs of sensitivity and nervousness in his early years. He was seriously upset after his illness and worried about the outcome. He felt continuously frustrated by the precautions which were taken for his health. Psychological symptoms often seen in disorders of the nervous system were present but interpretation was questionable.

CASE 5.—A boy of 7 years, 9 months, was admitted to the hospital because of tiredness, weakness, staggering, and fever and a diagnosis of poliomyelitis was made. There was one brother of 9 years. The child's development was normal; he talked and walked at 11 months. Doing well in third grade, he was considered shy and nervous.

During his stay in the hospital, he was drowsy, uncooperative, and violently resistive to back packs. He was considered noisy and used bad language. Question of encephalitic behavior was raised by the House Staff and psychologist and psychiatrist were consulted. They found him rather apprehensive, resistant, and disturbed about the whole situation rather than mentally confused. Later he ceased to resist packs and was considered friendly when given his own way.

He was discharged after four weeks to complete bed rest at home for two weeks and then to be followed in orthopedic clinic.

Four Weeks After Discharge.—He was playing very actively the whole day long, was impertinent to mother, and had recurring abdominal pains of unknown cause.

Six Weeks After Discharge.—He went back to school. He burst into tears when confronted with work that the class had learned during his absence. He received poor marks because of his inability to complete the necessary make-up work. He was under pressure both

at school and at home due to poor marks, was distressed about his marks, and said he hated school. (Conference of social worker with teacher.)

February, 1944, Three Months After Discharge.—He was doing fair work, was pushing himself hard. Most of the arithmetic was made up. The child still had pains in his arm but mother considered him less upset generally.

April, 1944, Five Months After Discharge.—Psychologist's notes: Tense child, friendly, ambitious. In lengthy tasks he still gets fatigued easily. He has an intelligent approach to problems but exhausts himself in an effort to solve them expertly. Revised Stanford gives an I. Q. of approximately 100 with wide scatter. He has reasoning ability on 8- and 9-year-old level in problems which can be solved quickly and intuitively. Memory for facts is on a 10-year-old level. He fails on 7- and 8-year-old level when patient construction and following of directions are called for, has difficulty in learning new materials and in visuo-motor functions, and writes poorly. One senses that this child is not yet functioning to the best of his abilities. Mother finds him still difficult and easily upset. His feelings are hurt easily and he "has lost all sense of humor." He likes physical exercise but gets fatigued from climbing. He is impatient, tempestuous, jealous, and weepy.

June, 1944, Two Months Later.—Psychologist's notes: Mother reports conflict between boy and father; boy regarded as jealous of father. Patient is evidently mother's favorite.

October, 1944, Four Months Later.—A psychological interview reports improvement in learning habits and attention spans, and better endurance; he is rather poor in visuo-motor functions but improvement is noted. His I. Q. is 110. He seems more at peace with the world. He had one major incident in school—got into a fight with a boy and called the principal names. Other than this, school finds him improving and doing good fourth-grade work. Mother considers him less tempestuous and easier to live with.

April, 1945.—After a six-month interval another psychological interview reports: Considerable improvement; efficient and intelligent; better working habits; still best in immediate and intuitive learning; seems to have recuperated visuo-motor functions. The child looks happier. Mother works evenings while father is at home which "improves clothing budget of family" and "keeps peace in the house."

June, 1945.—Before going to camp he had a physical examination, and had no complaints. "Everything is fine since 1944." July, 1945, he fell off swing and broke his left arm. The child was very apprehensive. Within a month his wrist was in good condition but he missed out on going to camp. Sept. 13, 1945, he complained of stomach-aches. Sept. 21, 1945, he broke his arm again. Sept. 27, 1945, he still complained of undetermined stomach-aches. October, 1945, he had continued stomach-aches. The boy stated that these aches have bothered him for a year and a half. In November, 1945, the arm was in good condition but the family was upset. In January, 1946, the case was reopened with social service at the request of the mother.

Summary.—This boy reacts quite violently emotionally to strain and sudden discomfort. The symptoms after polio and after broken arm are quite similar in various ways. After polio the child's resistance was considerably reduced. The psychological examination revealed for a period of 12 to 18 months, irregularities of functioning consistent with nervous system involvement.

II. Children who were more *seriously disabled* and needed consistent orthopedic care over a long period of time presented the following picture:

A. The *younger children* ranged from 18 months to 3 years of age at onset of illness. They were examined from one to several times within the first six months. Five of these patients were kept flat on their backs in an institutional environment. Generally speaking, they all seemed emotionally unstable, three of them being demanding and overactive and prone to temper tantrums. Two were subdued and too unenterprising for children of their age. In the psychological examination they showed hardly any evidence of mental progress since the

onset of illness. The youngest ones had made no appreciable gains in speech development and the older ones had failed to widen their vocabularies and use of language. All were unskilled in the handling of materials, some without initiative and desire to investigate and others being abrupt and impulsive. Handling of form material seemed particularly poor. When these children were later allowed out of bed for short periods they were extremely active and restless, tried to dash from one thing to another, and seemed interested only in their newly acquired abilities to get around and to feel free in space. A serious limp seemed to accelerate their desire for activity rather than hamper it. During this period of essentially stimulus-bound behavior, the children seemed to learn very little.

In the following years, every one of these children has presented some problem in development. After discharge from the institutions, considerable progress in emotional stability was noted in three out of five children. Those who were hyperactive during the first period have continued in this pattern. Though they quieted down somewhat, they still had rather poor working habits more than two years after the onset of the illness. The children with early speech retardation gained in vocabulary, though none has reached the standards of normal speech development within the period covered by this study.

CASE 6.—A girl of 1 year, 10 months, was hospitalized with complaint of drowsiness, listlessness, and involvement of lower extremities, and was given a diagnosis of poliomyelitis. A sister of 3 years, 6 months, and a brother of 1 month completed the family. The child had normal development and spoke about ten words at the time of illness. She was independent, fed herself, and could be trusted alone in the yard playing with dolls and sandbox.

During her stay in the hospital she seemed bewildered, shy, listless and unenterprising. After three weeks she was discharged to the convalescent home for further treatment. She was unable to sit or stand. During the stay in the convalescent home she was kept in bed in a dormitory with other small children, some of whom were more active than she. She was considered unenterprising and did not resist when other children grabbed her toys. The general impression was that she was retarded.

May, 1944, Seven Months After Discharge.—Psychological notes: Child cannot come up to a sitting position but sits for short periods supported, though not often. Is considered "good as gold" by nurses, though they feel that she is retarded. Seems friendly, very quiet and passive but with "sparkle in the eyes." She enjoys test materials, is quite unskilled with them, and does not resist when they are taken away. Does not talk spontaneously but repeats what is said to her and points toward pictures about which she is being asked. Imitates very poorly. Adaptive behavior and language development approximately on a 2-year-old level (Gesell Schedule). Her chronological age is 2 years, 6 months.

October, 1944.—She was discharged home on the insistence of parents. She could not pull up to a sitting position, or walk, or stand alone. Great lack of self-confidence. Is considered timid and unenterprising.

November, 1944.—A social worker reports that the child is blossoming, although still not walking independently.

January, 1945.—Psychological note: She walks alone at home, but during hospital visit would walk only with support. The left leg is seriously involved. The child has a good vocabulary and good verbal comprehension but is slow in using speech herself. She is able to speak in sentences but does not use them conversationally, only to indicate direct wants. She is rather slow in adapting to new tasks, likes to repeat the activities she knows, and does poorly in recognition of forms, formboards, and drawing. In formal tests, however, she reaches a mental age of 3 years, 5 months, and an I. Q. of over 100. (Rev. Stanford-Binet.)

September, 1945.—Psychological examination in home: She is still rather passive and immature in attitude but is interested. She does not use much initiative but prefers tasks in which the solution presents itself. She is still not too good in visuo-motor tasks but has improved in language comprehension and use of language. The mother, who is intelligent and a good observer, considers her oversensitive and delicate emotionally.

September, 1946.—The child has gained in self-confidence and good humor though she remains sensitive and passive. She is up to age level (chronological age, 4 years, 10 months) in formal tests, though not good in answering abstract questions. She still seems immature and impractical, lacking in general interest for everyday information. She entered Sunday school but did not stay because she was bewildered and confused. Mother would like to be reassured about her mental abilities. She thinks that the child is "quite smart about a lot of things" but sometimes requires much time before she understands.

Summary.—This child's development from onset of illness has been very irregular. During the long period of hospitalization and immobilization the child has become passive and unenterprising and her speech development was retarded. She improved after returning home but continued to have some difficulties in form comprehension and other abstract functions.

CASE 7.—This boy of 3 years was admitted to the hospital with the complaint of vomiting, fever, and stiff neck of two days' duration. For a week prior to admission he had been irritable and ate poorly. There is one younger brother in the family. The patient developed normally, walked at 10 months, and talked soon after. He was never a feeding problem, was healthy, usually played vigorously, was never irritable, but was a little timid with strangers.

During his hospital stay he was quite listless and drowsy, retiring from contact. He talked very little and seemed bewildered and afraid. Later he seemed more cheerful and brighter but often was noisy and uncooperative. He was discharged to convalescent home after a 3-week hospital stay, with considerable paralysis of the right leg.

From October, 1943, until July, 1944, the child was in the convalescent home, where his behavior was described as very uncooperative, difficult to manage, sullen, and unhappy, very much in need of affection, noisy, and resistive. He was the "bad boy" of his group.

May, 1944.—Psychological note: Child is excitable, easily frustrated, but responsive to kind handling. He talks fluently, has an adequate vocabulary and quick responses but his enunciation is quite poor. His general behavior level is approximately 3 years. He is very impatient and often too unstable to follow directions adequately.

October, 1944.—He is at home, happy and robust. He is easily overexuberant, gets around at great speed with braces, seems less easily frustrated than in summer, but still does not like failure. He talks a good deal. Mother finds his speech improved since he returned home. While at the convalescent home he stuttered quite a bit and spoke indistinctly. During the examination the child becomes quite aggressive when the convalescent home is mentioned and declares, "I am not going there." General impression: good language behavior, good comprehension, but considerably better in gross motor activity than in fine motor tasks, impatient with fine motor work, draws very poorly, has visuo-motor difficulties, but is good in formboards. Attention spans for directed work are not good but are better for games; he seems alert and happy. Since the child has been away from home so much and has had more than enough social experience, nursery school was not considered wise at the time.

September, 1945.—The patient gets around with a brace. He is very active and lively. He likes to jump and has frequently broken his brace. He seems immature in attitude, timid, and embarrassed, but more friendly as time goes on. He seems insecure about his own ability and avoids difficult tasks. His speech is almost clear. He has a good vocabulary, but is poor in responses to meaningful abstract questions. His drawing is still very poor. Mental age on Revised Stanford-Binet is 4 years, 2 months (C. A., 5 years, 0 month), and I. Q. is 80 to 85, approximately.

September, 1946.—He goes to first grade, seems steadier in attitude, is friendly and cooperative but still quite immature and easily embarrassed and still does very poorly in block-

building (imitation), drawing, Goldstein Stick Test, and number concepts. Mental age on Revised Stanford Binet is 5 years, 0 months, I. Q. is approximately 80 to 85 (C. A., 6 years, 0 months).

Summary.—This child had ben a vigorous, robust, and well-developed boy before illness. He reacted rather violently toward hospitalization and motor restrictions. He had a difficult period of social adjustment for a year after illness, improved after returning home, but showed an irregular and not altogether satisfactory development.

B. The findings on the group of *older children with serious paralytic involvement** are rather incomplete. For most of these children, the realization that their disability would be permanent came very gradually. During the acute stage of the illness they knew that they were the victims of the "dread disease" polio and many were aware of the distress of their parents. Ordinarily, however, their attitude seemed characterized by the idea that they were acutely ill, and that treatment was being given which would lead to complete recovery in due time. Being all together in one open ward, they felt they were members of a group equally afflicted. They saw new children constantly coming in and others being discharged as recovered. They started to realize what was happening to them in general only when, after a time in the convalescent home, progress seemed to slow down considerably. Many of them still remained relatively cheerful as long as they stayed together and remained members of a group. A completely new period, however, was to arise for them, when it was time to rejoin their families and to adjust back to ordinary ways of living.

Problems centered around the individual's gradual adjustment to his situation as a handicapped individual cross the borderline areas between psychology and psychiatry and clearly belong in the field of psychiatry. Therefore, they go beyond the scope of this study. Furthermore, practical considerations had their limiting effect. The staff psychiatrist of one of the convalescent homes became particularly interested in the adjustment problems of these children. Apart from his special qualifications, he had the added advantage of being able to see the children informally and almost constantly. Because of this overlapping of interests it seemed wise to abandon the psychological evaluation of nine of these children.

Psychological examinations, however, were given to a group of eleven older children at the other convalescent home. Five of these children were still on complete bed rest, whereas six others were able to get around on crutches and braces. Psychological examination of these children within the first nine months revealed normal performances in the conventional intelligence tests. Six of these children did poorly in tests involving form comprehension and analysis. Four had serious difficulty in copying of forms, memory for forms, and in formboard tests. Six had much trouble in sustaining attention in prolonged tasks. This seemed particularly distressing in several cases in which the children had been considered bright and intellectually able, and in which the poor school progress after illness added a new disappointment to the distress over the physical handicap.

*Patients with bulbar involvement and acute respiratory distress are not included in this analysis.

CASE 8.—This girl of 6 years was admitted to the hospital with weakness in right leg, fever, and pains in back and neck. She was given a diagnosis of poliomyelitis. There were two older sisters, the second of whom had a thyroid deficiency and was retarded in development. The patient's development was entirely normal and she was regarded by parents as the brightest of the family. She tried to imitate her oldest sister and seemed quite precocious to parents in certain ways. She was interested in letters, knew how to spell, and was scheduled to enter school in the fall. A high-strung, lively child with occasional nightmares, she was somewhat fussy in eating habits.

During her hospital stay she was very irritable, negativistic, uncooperative, and uncommunicative with male doctors, but she established friendly relationships with all women. When no man was in sight she became talkative and humorous. She was responsive and apparently of good intelligence. She was discharged after three weeks to the convalescent home with considerable involvement of right leg.

June, 1944, Seven Months Later.—In convalescent home she gets along on crutches, is friendly and a little excitable. In psychological examination her mental level is revealed as slightly below average. She has some speech defect, enunciates poorly, has poor working habits, and short attention spans, is very poor in visuo-motor functions, copies forms badly, and is poor in Kohs Block Design Tests. She has some schooling but does not know how to read and has no number concepts. She has friendly, sociable manners.

September, 1945.—The child is back home; she is in second grade but still does not read. The parents are quite bewildered since they feel that in school matters, she has forgotten what she knew two years ago. Mother states explicitly, "We always thought J. was the smartest of our children. She was early in everything and now she does not seem bright."

September, 1946.—The child now walks with a limp, likes to leave crutches off, and gets around without them. She roller-skates, etc. Her speech is now fluent and of better quality. She is very talkative and quick in her answers, rating a mental age of 8 years, 4 months, on Stanford-Binet with an I.Q. of approximately 90 to 95 (C. A., 9 years, 1 month). She is still very poor in memory for designs tests and in Kohs Block Design Tests.

She is unsystematic and inconsistent in her working habits and impulsive in her reactions. She continues to have poor marks in reading and arithmetic. She is doing well in everyday matters and seems alert and responsive, though she is considered quick-tempered and moody, being either irritable or exuberant.

Summary.—This child was apparently getting along well and at the age of 6 had shown interest in school matters. After her illness she displayed irregular working habits and poor visuo-motor functions which, for over 2 years, interfered with her progress in reading.

CASE 9.—A boy of 7 years, 2 months, was admitted to the hospital with fever, drowsiness, and stiff neck. He seemed oriented but dopey. A diagnosis of polioencephalitis was made. Development was said to be normal; he walked at one year and talked early. He was always lively but not difficult. He was in the first grade and promoted to the second.

After a hospital stay of nearly two months he was discharged to a convalescent home with serious sternomastoid involvement.

June, 1944, Nine Months After Discharge.—Considered "retarded" in the convalescent home. Psychological notes: Very short attention spans, learning difficulties, gets fatigued and confused quite easily, reasoning ability in some short tasks seems to be essentially adequate though general mental picture still rather unsatisfactory. Very poor in visuo-motor tasks; unable to read. Schoolteacher in home considers him "practically unteachable."

January, 1945.—Child is home. He is improved but still has a stiff neck and tries to support his head with his hand. Seems to get fatigued very quickly. Mother is upset and slightly impatient with his poor progress and his teacher is at the "end of her rope." The child's attention is variable and his marks range between 16 and 96. He is difficult to handle at home, cries easily, and is "like a baby." Psychological examination shows some improvement. Has rather good effort, but attention spans still short. He becomes restless easily.

Test results: Stanford-Binet gives a mental age of 7 years, 4 months (C. A., 8 years, 6 months), I.Q., approximately 80. Does poorly in Kohs Block Design Tests and in Good-enough Drawing Tests.

October, 1945.—He is in the third grade but still not reading on first grade level. His attitude seems considerably improved. His movements are quieter and he seems more stable altogether. Mother finds him easier to handle and finds that he is able to take quite some responsibility with the younger children. Psychological examination: Quality improved, better attention spans, more regular performance, still considerable visuo-motor difficulty, though improving. "Reversals" in reading are prominent. The sternomastoid involvement still is quite evident.

Summary.—This child's development after illness presented a picture often seen in children with polioencephalitis. Irritability, short attention spans, difficulty in concentration, and difficulty in the visuo-motor functions were quite prominent. His condition improved gradually, aided by careful avoidance of strain. The physical handicap was an added complicating factor in his readjustment.

DISCUSSION

In the following, the findings will be summarized and discussed briefly. Some of the results are more or less specifically related to the disease of poliomyelitis and its treatment, while others are similar to those found in any situation requiring the child's sudden separation from his customary environment under conditions of strain. Still others can be duplicated in any pediatric condition calling for institutionalization, immobilization, medical procedure, and adjustment to a more or less permanent physical handicap.

In the psychological examination, a high percentage of children clinically recovered from poliomyelitis insofar as motor disability is concerned, reveal *qualitative difficulties in mental functioning* which, as a rule, do not show in the conventional type of intelligence test but can be detected through specialized procedures. Some of the psychological symptoms are irritability, fatigability, and fleeting attention. Others are difficulties in the process of abstraction, which becomes most evident in certain visuo-motor functions. These difficulties may persist for a prolonged period. They are particularly evident in cases in which the question of encephalitic involvement was raised at the acute stage of the illness. To some degree, they are present in cases in which the medical history notes drowsiness, severe headache, and, in some instances, only nausea at the onset. In younger children, such disabilities often may hamper the formation of desirable working habits and the general adjustment to school and its demands. In older children who have already formed reading and working habits, the same disturbances may slow down the child's progress and be irritating and annoying to child and teacher. The earlier the child goes back to school the more he is likely to get into serious complications. This is particularly true when parents and teachers endeavor to have the child catch up on lost school time.

Children in a group followed in Boston were, as a rule, kept out of school for a longer period of time than those in New Haven. In most of these cases, a home teacher was able to make allowances for short attention spans and other difficulties through individual attention and shorter working periods. For this reason their learning difficulties seem to complicate their life to a less serious degree.

Sudden hospitalization, often under conditions of panic, and separation from home, are likely to create a medium for the development of emotional problems. This is particularly the case with younger children who go through the upsetting experience of being handled by strangers at a time when they are most in need of their mothers' comforting attention. Not being able to understand explanations, they do not know what is happening to them. The effects of a hospital experience are often felt for a prolonged period after discharge and may manifest themselves in a variety of symptoms such as restlessness at night, increased dependency on parents, irritability, and timidity with strangers. Similar problems have been described and are encountered daily in the experience of all those dealing with hospitalization of young children. In the case of children recovering from poliomyelitis, the emotional status of the parents is an added complicating factor which cannot be overlooked. In many instances the child discharged from the hospital returns to a mother who is barely recovering from the shock of the child's sudden illness. Completely exhausted, she is often unable to cope with the new emotional problems evolving in the care of her child. Tensions between a still convalescing child and his mother are also found in the older age groups. More rigid and prolonged medical supervision has, apart from the orthopedic value, the advantage of protecting the child from strenuous outside competition. It is more likely, however, to create new anxieties and resultant frictions between children and mothers than is the case in a more liberal regime. A good many difficulties with younger and older children center around the doctor's prescription of restricted activity, hot baths, and exercises. Depending on their own emotional make-up and on the impressiveness of the doctor, many parents feel compelled to follow these directions as accurately as possible, often more so than intended by the physician. Such meticulous adherence to doctors' orders appears in the children's eyes as either an almost intolerable new excess of parental authority or as an incomprehensible diminution of parental might. This is deeply resented by some children. In most cases of emotional difficulties resulting from hospitalization and after-treatment rather than from the child's handicap itself, psychological guidance has proved useful and has given mothers and children the opportunity to discuss and readjust their differences.

Prolonged hospitalization and immobilization do not fail to have their undesirable effects on the general development of the young children of the group under discussion. Despite expert nursing care, the babies have to forego the individualized constant affection to which their age entitles them. They have to share with others the attentions of all-too-busy nurses who usually are only able to give to every baby enough time for the necessary routine procedures but not enough for leisurely fondling. As in all institutional setups, a few of the babies become "everybody's darling" whereas others have to look on. Still other children have to live up to their once-established reputation of being "bad" and are forced to get their share of attention through such devious means. In this respect, interesting shifts of moral standards are observed among children and nurses. Since, from the orthopedic point of view, it is desirable to prevent as much motion as possible, being "good" means being quiet and unenterprising while being "bad" means indulging in the most modest imitations of a pre-

school child's normal activity. A good deal has been written in recent years about the ill effects of institutionalization and immobilization of babies on emotional and social development.[4] From the standpoint of developmental psychology a few considerations may be added here. Retardation of speech development has been noted by several observers as one of the evils of institutional living. It has been pointed out that children living in an institution do not have much opportunity to develop language as a social function since they do not have much individual contact with adults. It has also been found that children living in a children's groups get along on a rather restricted vocabulary. To the consideration of these social functions of language, one may add that the normal child, by hearing new words and by meeting new objects with new names daily, widens the scope of his language. Life for a child confined to a hospital bed lacks these possibilities. The same dearth in normal experiences becomes acute in other developmental aspects. A normal child gradually discovers space and its properties through his own activities during the first two years of his life. His sensory-motor experiences are, as pointed out by Piaget,[11, 12] Gesell,[5] and other psychologists, at the basis of his intellectual development. In a constant process of adaptation, the child's activity patterns are shaped through the interaction between the child and his environment. In simpler words, it is his ability to get around and to handle objects which brings him into contact with an ever widening world of objects. A child confined to his bed and often in a cast or on a frame, lives in a seriously restricted world.* It is interesting to observe the behavior of a good many babies who are or who have been more or less recently immobilized for prolonged periods. Their world having been confined to the restricted sphere of their immediate neighborhood, some of them remain aloof from all events and happenings taking place at any distance; others do not even try to go after an object which with some effort would be well within their reach. In this respect, as well as in others concerning the effects of hospitalization and immobilization, only follow-up studies over a period of years will determine whether or not permanent deviations of mental development will result.

SUMMARY

1. A group of fifty-two children with poliomyelitis were followed by regular interviews and psychological examinations for three years.

2. Those patients who made a complete recovery from the motor effects of the disease were likely to be emotionally fragile and often showed psychological symptoms suggesting cerebral involvement. These difficulties combined with the emotional upheaval created by the illness resulted in many problems.

3. Those patients who developed sufficient motor disability to require prolonged hospitalization and orthopedic care showed certain characteristic disturbances:

a. Those in the age-group one to five years were found to have an irregular mental development. During the first years of hospitalization, a lag in speech

*In some instances, enterprising nurses singled out an occasional child and provided him systematically with social, visual and auditory experiences. Such attempts highly applauded and encouraged by all those interested in psychological aspects, have rewarding results and prove effective in mitigating some of the problems of the immobilized child.

development was particularly noted. Difficulty in comprehension of object relationships was noted. Unsatisfactory emotional adjustment was observed, which improved gradually after the child's discharge to the home, but in most cases left some marks upon the patient's personality development.

b. Those in the age group five years and over showed varying symptoms, ranging from short attention spans, difficulty in concentration and resulting learning difficulties to more specific disturbances in functions of abstraction suggesting nervous system involvement. General emotional fragility was also quite evident. All these signs were prominent during the first year. After this, they tended to recede, though traces were still discernible for several years.

4. This study suggests that poliomyelitis, first as a specific infection of the central nervous system and second, as a crippling disease leading to prolonged hospitalization and immobilization, tends to produce interference with normal mental and emotional development.

5. On the basis of this study, it is recommended that greater attention be paid to psychological factors in the care of these children as follows:

a. Careful psychological appraisal of children recovering from poliomyelitis will be useful in order to protect the recovering child from undue mental strain.

b. Supportive technique during the period of readjustment of the child to the home may help relieve parents' anxieties and children's emotional problems in the convalescent period.

c. Special programs devised to compensate the hospitalized and immobilized child for restricted experiences will be useful in mitigating problems in emotional, mental, and social development.

REFERENCES

1. Copelman, F.: Follow-up of One Hundred Children With Poliomyelitis, The Family, Family Welfare Assoc. of America, Dec., 1944.
2. Crothers, B.: A Pediatrician in Search of Mental Hygiene, N. Y., 1937, The Commonwealth Fund.
3. Crothers, B., and Meyer, E.: The Psychologic and Psychiatric Implications of Poliomyelitis, J. PEDIAT. 28: 324, 1946.
4. Freud, A., and Burlingame: Infants Without Families, N. Y., 1944, International U. Press.
5. Gesell, A.: The First Five Years of Life, N. Y., 1940, Harper & Bros.
6. Goldstein, K., and Scheerer, M.: Abstract and Concrete Behavior, Psychol. Monogr. 53: 2, 1944.
7. Grant, A.: Medical Social Work in an Epidemic of Poliomyelitis, J. PEDIAT. 24: 691, 1944.
8. Lord, E.: Children Handicapped by Cerebral Palsy, N. Y., 1937, Commonwealth Fund.
9. Lord, E., and Wood, L.: Diagnostic Values in a Visuo-Motor Test, Am. J. Orthopsych. 12: 414, 1942.
10. Meyer, E., and Simmel, M.: Psychological Appraisal of Children With Neurological Disorders J. Abn. & Soc. Psychol. 42: No. 2, 1947.
11. Piaget, J.: La Naissance de l'Intelligence chez l'Enfant, Neuchatel and Paris, Delachaux and Niestle, 1936.
12. Piaget, J.: Principal Factors Determining Intellectual Evolution from Childhood to Adult Life, Harvard University Press, 1937.
13. Stanfield, C. E.: Personality Repercussions of Anterior Poliomyelitis. A Review of the Literature, Am. J. M. Sc. 213: 109, 1947.

A NOTE ON EXPERIENCES WITH A ROOMING-IN ARRANGEMENT FOR NEWBORN INFANTS IN A SMALL HOSPITAL

HENRY L. BARNETT, M.D.
NEW YORK, N. Y.

THERE has been increasing interest recently in a new departure in hospital procedure which allows the newborn infant to reside in the mother's room during a greater part of the postpartum period.[1, 2, 3, 4] This stems from the increasing emphasis placed upon the newborn period as an important experience in the emotional development of both infant and mother. Interest in this so-called "rooming-in" arrangement has been stimulated also by the increasing attention of the pediatrician to the developmental problems of the well baby. The arrangement permits the pediatrician, obstetrician, and nursing staff to observe and perhaps help in solving some of the problems which, with customary arrangements, are postponed until the mother is at home, and in a certain sense, alone.

A rooming-in arrangement for newborn infants was employed in the twelve bed maternity ward of the hospital at the atomic bomb project at Los Alamos, N. Mex. No systematic observations or accurate record of the reactions to the arrangement were made. However, general observations and interest in these reactions were sustained over a period of two years, and certain definite impressions were gained. The scarcity of such studies has prompted this note on experiences with a rooming-in arrangement in a small hospital. Establishing the soundness of these impressions and the application of the arrangement to a large maternity service will require more extensive and precise observations.

The obstetric ward of the 120-bed hospital at Los Alamos was a separate wing consisting of a nursery with a preparation and formula room and six double rooms with individual baths. During the two-year period of observations, the number of deliveries averaged twelve to fifteen per month.

Infants were admitted to the nursery from the delivery room and usually remained there for the first day after birth. The actual practice of the rooming-in arrangement was flexible. The daily period the infants were in the mothers' rooms was decided entirely by the individual mothers; it varied considerably with different mothers and on different days with the same mother. The infants were always returned to the nursery during the night.

There were no separate cubicles for the babies in the mothers' rooms. Two mothers and two babies usually occupied each room. The attempt was made to group mothers with babies of approximately the same age in the same room. A bassinet with a high stand was kept beside the bed of each mother in a position where she could see and reach the baby. The sides of the bassinet were of one-half inch spaced ribs, which allowed the mother to see the baby in it.

From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

The reactions of both the patients and the professional personnel to the arrangement as described were almost unanimously favorable. These reactions may be defined in terms of the participants.

The Babies.—It was evident that even in this hospital which had proportionately more than the average number of nurses, the infants received more attention than would have been possible with the usual nursery arrangement. Considerably less crying and fewer periods of prolonged crying resulted. The self-demand feeding schedule advocated by the pediatrician was followed with more or less modification by most mothers. This type of feeding schedule could not be adapted to the usual nursery arrangement, but followed naturally as the result of the rooming-in arrangement, and it also contributed to the decrease in crying. There was a tendency for mothers to disturb their infants more frequently than seemed reasonable. This tendency was remedied by describing the usual sleeping behavior of infants and by the quick realization of mothers that there was considerable infantile activity which did not require their attention.

There was no apparent increase in the incidence of infections. On the contrary, the frequent examination and persistent observation of the babies by the mothers perhaps brought possible sources of infection to the attention of the pediatrician more quickly than would otherwise have been the case. This earlier recognition of communicable diseases, if substantiated, may be of especial importance.

No definite influence of the rooming-in arrangement on the number of successfully breast-fed infants could be ascertained.

The Mothers.—Mothers, especially those having their first babies, expressed almost unanimous approval and enthusiasm for the arrangement. The initial reaction of most women who had had children previously was that they wanted to rest during this "vacation" from the care of their older children. It was surprising, however, how short a "vacation" most of them really wanted. Although they did request to have their newborn babies in their rooms less than the mothers of first babies, on the whole they were also eager to "get started" with the new one.

During the early post-partum days, there was a tendency for some mothers to want their babies in the room for longer periods and to attempt to do more for them than seemed advisable to the obstetrician, but this offered no real difficulty. There may even have been an element of compulsion on the part of some mothers, as a result of the previous discussions about the arrangement,* to prove to the pediatrician (and/or to themselves) that they really did want to have the baby there.

*The type of development and the inherent characteristics of the community at Los Alamos offered a unique opportunity to put some pediatric principles into dynamic action. This was particularly related to the type of community projects which could be carried out. One of these was the prenatal conferences between the prospective parent (or parents) and the pediatrician. Ten or twelve pairs of prospective parents were invited to a series of three general discussions held during the second trimester of the wife's pregnancy. These were followed, if requested by the parents, by individual conferences during the last trimester. At one of the former of these, something of the general procedure at the time of delivery was described and the rooming-in arrangement discussed. These group conferences were usually limited to expectant parents of first children since their interests at this time were in general different from those of parents with older children. The latter were seen individually.

The usual sequence of events with the rooming-in arrangement was a request by most mothers to have their babies in the rooms shortly after the delivery; less eagerness on the second day; and on the third day a dampening of enthusiasm. The last was ascribable to a combination of circumstances: physical discomfort of painful breasts and healing episiotomy; subsidence of the feelings of elation and relief over the successful termination of the pregnancy; direct manifestations from the baby that he was not yet getting enough milk precipitating a sudden anxiety over the actual beginning responsibility for the baby; and perhaps other factors. Thereafter there was almost always a rapidly increasing desire to have the baby in the room most of the day.

After the fifth or sixth day, the mothers assumed a large share of the care of the infants. Sufficient supplies were kept in the mother's bedside cabinet so that she could change the diapers and dress the baby without calling the nurse. Babies were breast fed without assistance but, because of lack of facilities for storing or warming bottles in the rooms, it was necessary for mothers of bottle-fed infants to request the nurse to bring the feedings.

The mothers were impressed by the fact that they were learning these techniques by doing them. In place of the usual "demonstrations" they were actually first shown, then helped, and then corrected in their techniques. They appreciated that they were really learning these procedures under the best possible guidance.

The Doctors.—As observed by the pediatrician, the greatest single advantage of the arrangement was the feeling of confidence exhibited by mothers of first babies upon leaving the hospital. This confidence was in striking contrast to the trepidation of most mothers of first babies leaving a hospital with the usual nursery arrangement. Closer contact between mother and pediatrician during the newborn period, which the rooming-in arrangement demands, and actual experience of the mother with the baby undoubtedly contributed jointly to this increased confidence. There was rarely an instance during the first few days at home of "the baby cries so much and he never did in the hospital—what am I doing wrong?" These mothers had observed how much and how often their babies cried in the hospital despite the expert care of trained and experienced pediatric nurses and the close supervision of the pediatrician.

The arrangement provided an unexcelled opportunity for the pediatrician to observe the mother and baby together. From these observations and those of the nurses, the pediatrician gained insight and understanding of individual mothers and babies which aided his later interpretation of their developmental problems.

The close association between pediatrician and obstetrician* in carrying out the rooming-in arrangement clarified many problems which previously had been designated as obstetric or pediatric. As an example, before the arrangement was instituted, questions about breast feeding such as care of the breasts and the mother's general physical condition were considered almost entirely the

*Dr. James F. Nolan, St. Louis, Mo., as first head of the Los Alamos Hospital, made it possible to set up the rooming-in arrangement and, as the obstetrician, participated in it and contributed to its functioning by his understanding and cooperation.

responsibility of the obstetrician. Conversely, the pediatrician was almost independently responsible for the progress of the baby on breast feeding. These two obviously interrelated aspects of beginning breast feeding as well as other problems were found to be common ones in actuality, and this closer contact between mother, baby, obstetrician, and pediatrician contributed importantly to the value of the arrangement by fostering a real and joint interest in the problems of individual mothers and babies.

The Nurses.—The reactions of the nurses toward the arrangement were divided. The reasons for instituting it were discussed fully with all the participating nurses and they were for the most part accepted as reasonable. To some nurses the advantages seemed important enough to accept completely the new routine. Others were disturbed by the flexibility and "unorderliness" of the arrangement. The many requests and questions asked by mothers were time-consuming and often seemed superfluous to the nurses. It was impressed upon them, however, that these were obviously matters which concerned mothers, and merited respect as such, and should not be evaluated merely on the basis of reasonableness of the questions and requests.

In general, nurses' assignments did not appear to be materially altered by the arrangement. It is true that mothers' requests for more care for their infants than is usually given in a nursery increased nursing services during the first few days because mothers were unable to help, but this early increased expenditure of nursing time was amply compensated during the latter part of the hospital stay when most of the nursing care of the infants was taken over by the mothers.

Others.—The attitude of the fathers toward the arrangement was determined originally by their participation in the prenatal conferences, and it was favorable. During the period when the mother and baby were in the hospital after the delivery, the father's attitude usually seemed to reflect that of the mother. The chief reaction, therefore, was one of increased assurance that "everything was going well."

As would be expected, the opinions of the friends and relatives of the mothers about the wisdom of the arrangement were transmitted to the mothers. The arrangement also influenced visiting. Although the doctors did not emphasize it, mothers felt strongly that they should not have visitors while the baby was in the room. Since babies were in the rooms most of the day, by the time the mothers felt well enough to have visitors daytime visiting was practically eliminated. Handling and caring for the baby allayed the customary boredom of the second week in the hospital, and visitors were not needed for interest and stimulation. As a result, mothers probably derived more rest and relaxation than during routinely conducted post-partum periods.

SUMMARY

A rooming-in arrangement for newborns was employed for a period of two years in a twelve-bed maternity service of a small hospital at Los Alamos, N. Mex. The arrangement is described and the reactions of participants discussed.

Favorable impressions were gained of both the desirability and feasibility of the rooming-in arrangement as applied to a small hospital. These impressions stemmed chiefly from the increased confidence with which mothers of first babies left the hospital and the closer participation of pediatrician, obstetrician, and nursing staff in observing and thereby helping to solve many of the problems which, with customary nursery arrangements, are postponed until the mother is at home, and, in a certain sense, alone. In addition, the arrangement provided an unexcelled opportunity for the pediatrician to observe the conduct of the mother with her newborn baby, and this insight contributed to his understanding and interpretation of subsequent developmental problems.

REFERENCES

1. Gesell, Arnold, and Ilg, Frances L.: Infant and Child in the Culture of Today, New York, 1943, Harper and Brothers, p. 82.
2. Simsarian, F. P., and McLendon, P. A.: Further Records of the Self-Demand Schedule in Infant Feeding, J. PEDIAT. 27: 109, 1945.
3. McLendon, P. A., and Parks, J.: Nurseries Designed for Modern Maternity, Mod. Hosp. 65: 46, 1945.
4. Report of the Committee on Infancy and Early Childhood of American Society for Research in Psychosomatic Problems. Attitudes of Women Toward Pregnancy and Newborn Baby, Psychosom. Med. 7: 224, 1945.

THE BLALOCK-TAUSSIG OPERATION

GEORGE W. SALMON, M.D., AND HOWARD T. BARKLEY, M.D.
HOUSTON, TEXAS

IT IS our purpose to review our experiences with the Blalock-Taussig operation in children* as an example of the results that may be obtained in the hands of others than its originators. It is not our purpose to review the experimental work upon which the operation is based, nor to discuss the diagnostic methods and surgical techniques involved. This already has been presented by the devisors of the operation in a very authoritative manner.[1, 2] In this report we have included all children in whom the chest was explored† (see Table I), regardless of whether or not the anastomosis was performed.

DIAGNOSTIC EFFORTS

The essential procedure of this operation is the construction of an "artificial" ductus arteriosus or a communication between the systemic and pulmonary circulations. By this means, an increased amount of blood is supplied to the pulmonary circulation, providing, of course, that the pressure in the systemic circulation is higher than that in the pulmonary circulation, so that the flow of blood will be from the former to the latter. As we interpret the problem, in a cyanotic child the essential diagnostic feature becomes an effort to ascertain whether or not there is a reduction in the amount of blood supplied to the pulmonary circulation.

In the history an important diagnostic point is delay in onset of cyanosis. This delay occurred in eight of the ten patients (see Table I); and in the two exceptions an accurate history as to this point could not be obtained. This suggests that the circulatory defect became much worse with the closure of a "normal" ductus arteriosus. A significant implication, therefore, is that the construction of a new ductus arteriosus might return the patient to an acyanotic state. We do not mean to imply that cyanosis is the injurious feature. It is rather anoxemia, of which cyanosis is a manifestation, which is deleterious to the patient.

In all of the patients, physical activity before operation was greatly limited, varying only in degree. Seven of the ten gave a history of syncopal attacks; such an attack usually followed exertion and an increase in the degree of cyanosis. These attacks were no doubt due to cerebral anoxia and were further evidence of the severity of the circulatory defect.

From the Baylor University College of Medicine, the Hermann Hospital, and the Junior League Children's Clinic, Houston.

*One of these cases is from the private practice of Dr. E. B. Brandes. Others were referred to the ward service by Drs. Brandes, Betty Moody, and Charles D. Reece.

†In all of these cases the anesthesia was administered by Dr. L. F. Schumacher, Jr.

The degree of cyanosis before operation varied from slight, with an increase upon exertion, to severe. Suffusion of the conjunctivae was present to a corresponding degree. The degree of clubbing of the fingers and toes also varied from slight to severe.

In eight of the patients there was a loud systolic murmur along the left sternal margin, heard best in either the second or third interspace; five of these eight had a corresponding thrill, one had a doubtful thrill, and two had no thrill. In one (E. C.) there was a soft, poorly localized, systolic murmur without an accompanying thrill. In one (G. S.) there was a systolic murmur heard best in the area between the left sternal margin and the left nipple; there was a corresponding thrill. Although we prefer that there be a systolic murmur along the left sternal margin, as described above in eight of the patients, such physical findings are not the most important part of the diagnosis. In tetralogy of Fallot, for example, the physical findings may be quite variable.[3] Of the two children (L. S. and K. B.) later found to have a patent "normal" ductus arteriosus of small diameter, neither had a continuous "machinery" murmur. Although we have employed the stethograph in some instances, we do not have a sufficient number of observations to warrant conclusions as to its value.

The results of the arterial blood analyses are tabulated in Table I. The specimens were obtained from the femoral artery; the blood was taken under oil, and heparin was added to prevent coagulation. The hemoglobin values mentioned are calculated from the oxygen capacity. The electrocardiograms showed right axis deviation in all of the patients except one (W. S.); in this exception the electrocardiogram showed left axis deviation.

Although in some of the patients the heart was slightly enlarged, in the majority it was of normal size (as measured by the cardiothoracic ratio). The location of the arch of the aorta was determined by its relation to the esophagus as demonstrated by a barium swallow (see Table I and Fig. 1). In all except one (D. W.) fluoroscopy of the chest before operation indicated absence of hilar pulsation, suggesting that the pulmonary blood flow was reduced in volume. None showed evidence of pulmonary congestion; congestion rarely occurs when the pulmonary blood flow is reduced.[4] Two of the patients with more severe conditions showed moderate pulmonary fibrosis.

In four of the patients the pulmonary conus appeared normal; in six it was not present. We have not operated upon a child having an unusually prominent pulmonary conus. In all except two (D. C. and D. W.) we have thought that the pulmonary arteries were demonstrably reduced in size; in these two exceptions we could not be sure. There was included, as a part of the estimation of the size of the pulmonary arteries, an anterior-oblique view for the pulmonary window.[4] If the pulmonary arteries are small this window may appear abnormally clear. The exact angle at which the oblique view is taken depends upon the location of the arch of the aorta. In most of the patients there has been roentgenographic evidence of enlargement of the right ventricle. In only two (E. C. and L. S.) has there been the boot-shaped configuration of the heart (see Fig. 1) considered classical of the tetralogy of Fallot.

TABLE I

CASE; AGE DATE OPERATED	ARTERIAL OXYGEN STUDIES: BEFORE OPERATION O_2 CONTENT (VOL. %)	O_2 CAPACITY (VOL. %)	O_2 SATURATION (%)	HB. (GM. %)	AFTER OPERATION O_2 CONTENT (VOL. %)	O_2 CAPACITY (VOL. %)	O_2 SATURATION (%)	HB. (GM. %)	AGE AT ONSET OF CYANOSIS (MO.)	SIDE OF ARCH OF AORTA	SIDE OF INCISION	SYSTEMIC ARTERY USED FOR ANASTOMOSIS	REMARKS
W. S.; 8 yr. 2/13/46	16.8	25.5	65.8	19.0	20.6 (5 mo. after operation)	23.6	87.2	17.6	12	Right	Left	Left subclavian direct from aorta	Defective development of right ventricle; electrocardiogram showed left axis deviation.
E. C.; 5 yr. 3/15/46	13.2	27.8	47.4	20.7					Unknown	Left	Right		Complete pul. atresia; unable to perform anastomosis; see text; discharged unchanged.
G. D.; 11 yr. 3/27/46	19.3	26.0	74.2	19.3	17.3 (3 mo. after operation)	18.9	91.5	14.1	1	Right	Left	Left subclavian direct from aorta	
L. S.; 3 yr. 4/19/46	18.9	28.6	68.1	21.2					18	Right	Left	Left subclavian direct from aorta	Died 24 hr. after operation; autopsy showed tetralogy of Fallot plus patent "normal" ductus of small diameter; cause of death undetermined.
E. M.; 11 yr. 5/22/46	18.6	29.5	63.0	22.0	20.2 (5 mo. after operation)	22.9	88.3	17.1	2	Left	Left	Left subclavian direct from aorta	
D. C.; 6 yr. 7/12/46	15.6	28.6	54.5	21.3	16.4 (3 mo. after operation)	28.3	58.2	21.1	7	Left	Left	Left subclavian direct from aorta	Was neither helped nor apparently harmed by anastomosis.
K. B.; 7 yr. 9/24/46	16.3	31.2	52.2	23.2	18.5 (10 days after operation)	26.6	69.7	19.8	9	Right	Left	Left subclavian of left-side innominate	A patent "normal" ductus of small diameter was found at operation; nevertheless, an "artificial" ductus was created.
G. S.; 8 yr. 10/9/46	17.2	39.5	43.7	29.5	18.7 (19 days after operation)	29.8	62.8	22.2	3	Left	Left	Left subclavian direct from aorta	
J. B.; 7 yr. 11/14/46	5.5	27.7	19.8	14.8					Indefinite	Right	Left		Truncus arteriosus communis; anastomosis not performed; died twenty-seven days after operation. See text.
D. W.; 6 yr. 1/9/47	12.5	31.8	39.4	23.7	21.3 (14 days after operation)	26.2	81.3	19.5	36	Left	Left	Left subclavian direct from aorta	

In those children in whom a fairly definite diagnosis could not be made, the chest was explored. If, at the time of exploration, a more definite diagnosis could not be made, the pressure in the pulmonary artery was measured. Of the patients in whom the pulmonary pressure was measured, the anastomosis was performed in one having a pressure higher than 300 mm. of water (D. C.; 340 mm.). This child has now been followed for seven months; he was not improved and was not apparently harmed.

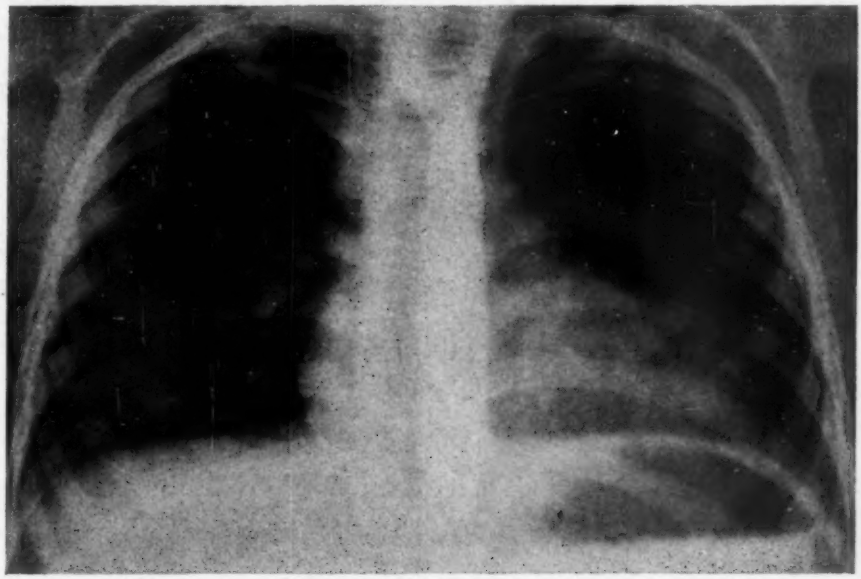


Fig. 1.—L. S. Chest plate with barium swallow to show right-sided arch of aorta.

One patient (G. D.) had a preoperative arterial oxygen saturation of 74.2 per cent. Ordinarily, we would not consider operating upon a child having a saturation this high. This patient had, however, been seen in one attack of heart failure and her history suggested several other such episodes. For this reason it was thought her outlook was poor and that the operation might be justified.

RESULTS

The postoperative course in most instances was surprisingly uneventful. Although we have included the administration of oxygen as a part of the routine postoperative management, in some of the patients it was discontinued within twenty-four to forty-eight hours. We have not used dicoumarol or heparin as a prophylactic measure to prevent thrombus formation. Penicillin has been administered routinely as a prophylactic measure to avoid infection.

A pneumothorax large enough to warrant intervention was noted on the second postoperative day in one patient (G. D.); after a single aspiration it

did not recur. Pleural effusion sufficient to warrant aspiration occurred in two (W. S. and E. M.); however, in neither was the effusion extensive or persistent. One (G. S.) developed laryngeal obstruction of a severity to require tracheotomy. This was no doubt caused by trauma from an ill-fitting endotracheal tube used during the operation. There have been no infections.

In four of the patients (G. D., D. C., G. S., and D. W.) in whom the anastomosis was performed, the pupil of the eye of the operated side became smaller at the time of operation. There has been no evidence of other elements of a Horner's syndrome. In none of these four has this pupil resumed its normal size. The hand of the arm supplied by the cut subclavian artery in every instance became cooler than the other. During the few months immediately following operation the temperature of the involved hand gradually rose to approach, but not completely attain, that of the other hand. In every instance in which the subclavian artery was cut, the circumference of the affected arm became and has remained smaller than the other. However, the use of this arm has been impaired but slightly, if at all. There has been no obvious correlation between the instances of pupillary change and the degree of coolness or wasting of the affected arm.

Of the ten patients in whom the chest was explored, the anastomosis was performed in eight. Six of these were remarkably improved. One (D. C.) was neither improved nor apparently harmed (his preoperative pulmonary artery pressure was 340 mm. of water). One (L. S.) died twenty-four hours after the operation. A necropsy showed tetralogy of Fallot plus a patent "normal" ductus arteriosus of small diameter. The actual cause of death, however, was not determined.

Of the ten patients the anastomosis was not performed in two. In one of these (E. C.) the findings at operation suggested complete pulmonary atresia. None of the arteries found in the hilus of the lung were large enough to accept an anastomosis with the subclavian artery. These findings bore out the preoperative diagnosis of inadequate pulmonary blood supply. The chest was closed and the child later discharged unharmed by the exploration. In the second patient (J. B.) in whom the anastomosis was not performed, it was found at operation that the pulmonary arteries and the large systemic arteries supplying the head and pectoral girdle arose from a large single trunk. Since the pulmonary arteries were apparently of adequate size, no anastomosis was performed. This patient had quite the most severe condition we have seen; her arterial oxygen saturation was only 19.8 per cent. Although she survived the exploration, she suffered widespread central nervous system damage occasioned either by widespread thromboses, or possibly anoxia, and died twenty-seven days later. Permission for an autopsy could not be obtained.

Each of the six who was improved is now enjoying activity approaching that of a normal child. None has experienced a recurrence of the syncopal attacks so common before operation. The alterations in the arterial oxygen studies are tabulated in Table I. In these six children, the average arterial oxygen saturation before operation was 56.4 per cent; after operation, 80.1 per cent. The cyanosis of the lips improved either at the time of operation

or in the immediate postoperative period. It was not always easy to be accurate about the exact time, because all received oxygen as already mentioned. The cyanosis of the nail beds may require several days to improve as may the suffusion of the conjunctivae. In one patient (G. S.) the cyanosis was not completely cleared but it was greatly improved. In all who have been followed for at least one month, the clubbing has begun to recede.

The anastomosis was performed in eight patients. In one the murmur became continuous and in two, almost continuous. In two the murmur became definitely longer. In two the murmur changed little, if at all. One (L. S.) died twenty-four hours after operation before any change could be accurately assayed. In these few cases there was only a crude correlation of change in murmur with degree of improvement of arterial oxygen saturation. Since operation there has been a slight increase in heart size (as measured by the cardiothoracic ratio) in some instances and little change in others. In most there has been an alteration in the contour of the heart in that the region of pulmonary conus has increased in size. Follow-up electrocardiograms have shown no change in axis deviation from that seen before operation.

COMMENT

Of these ten children in whom the chest has been opened, two have not survived. Although a 20 per cent mortality may seem prohibitive for any therapeutic procedure, it is hardly so when the severity of this disease is considered. In these cases the outlook for both longevity and normal activity (except in the mildest cases) is poor. Six children have been remarkably helped. In all likelihood an appreciable number of years has been added to the life expectancy. It is undeniable that these six are now leading more active, happier, more normal lives.

SUMMARY

Of ten children in whom the chest was opened to perform the Blalock-Taussig operation, six were remarkably improved. Of the remaining four (regardless of whether or not the anastomosis was performed) two were neither improved nor apparently harmed, and two did not survive.

REFERENCES

1. Blalock, A., and Taussig, H. B.: The Surgical Treatment of Malformations of the Heart in Which There Is Pulmonary Stenosis or Pulmonary Atresia, J. A. M. A. 128: 189, 1945.
2. Blalock, A.: Physiopathology and Surgical Treatment of Congenital Cardiovascular Defects, Bull. N. Y. Acad. Med. 22: 57, 1946.
3. Sidenberg, S. S., Kessler, M. M., and Wolpaw, R.: A Case of Tetralogy of Fallot With Absence of Cerebellar Vermis: Termination by Brain Abscess, J. PEDIAT. 28: 719, 1946.
4. Taussig, H. B.: As quoted in (1) above.

HOMOLOGOUS SERUM HEPATITIS FOLLOWING TRANSFUSION IN AN INFANT

LIEUTENANT HENRY B. BRUYN (J.G.), MEDICAL CORPS,
UNITED STATES NAVAL RESERVE (INACTIVE)*
BERKELEY, CALIF.

HOMOLOGOUS serum hepatitis has been defined,[1] as a disease, "produced by parenteral inoculation of whole blood, serum, or plasma, ordinarily obtained from an individual who is supposedly nonjaundiced, or at least a donor not known to be ill with infectious hepatitis." This condition is differentiated at present from infectious hepatitis, which, although also capable of transmission parenterally through blood or blood products, may, in addition, be transmitted through the feces and orally.

These clinical entities have become of increasing importance in recent years, especially in the experience of military medicine. Cases of epidemic hepatitis have been recorded among soldiers of almost every war since the War of 1812 with increasing frequency.[2] The recent war has brought about not only a clarification of the etiology of this disease and its relationship to "acute catarrhal jaundice," but it has also brought into prominence means of transmission of this disease other than by contact. With the extensive use of pooled plasma and whole blood, post-transfusional hepatitis has become recognized not only as a definite disease but also as a hazard.[3-11] Drying and freezing the blood product does not eliminate the agent of transmission.[5] The pooling of plasma, both commercially and in hospital blood banks, obviously increases the chances of transfusing a patient with material from a donor carrying the virus in his blood.[12] In 2,040 hospital patients transfused with pooled plasma, Spurling and Vaughn[13] found an incidence of homologous serum hepatitis of 7.3 per cent, while in 1,284 patients transfused with unpooled whole blood there were no cases. The donor who is the source of transmitted infectious hepatitis may be undetected either through failure to elicit from him a history of jaundice or through his having infectious hepatitis without either icterus or symptom.[11, 14]

It should not be implied, however, that homologous serum hepatitis is a new condition, for as early as 1885, Lurman (cited in[4]) noted an outbreak of jaundice among shipyard workers in Germany following vaccination with "glyceranated, humanized lymph." The British workers[4] have described the occurrence, in 1937, of an outbreak of jaundice in patients inoculated with a certain lot of measles convalescent serum. Since then there has been an extensive series of papers and reports, from both England and America, of jaundice following the use of yellow fever vaccines which contained human serum.[3, 4, 15, 16] It was very soon apparent that these cases of jaundice were analogous to those appearing after plasma and blood transfusion.[4-7, 11]

It has been demonstrated that this disease is due to a filterable agent, probably a virus, which is similar to, but not identical to, the virus of infectious

*Fellow in Research, Department of Medicine, University of California Medical School, San Francisco.

hepatitis.[17, 18] The distinct epidemiologic and immunologic differences between the two have been summarized by Neefe and associates[19] and for the present purposes it will suffice to say that both agents are filtrable, resistant to 56° C. for thirty minutes, and transmissible to volunteers. The agent of homologous serum hepatitis is found in the serum of patients ill with the disease and throughout the incubation period. Some observers[20] have demonstrated its presence in the nasopharyngeal washings during the acute phase of the disease, although this work has not been confirmed by other workers. It has not been found in the feces, in contrast to the virus of epidemic hepatitis. There is an immunity developed following homologous serum hepatitis which does not protect against epidemic hepatitis.[19]

One of the apparent important differences between infectious hepatitis and homologous serum hepatitis is the length of the incubation period, which in the former is from fourteen to forty days from exposure to jaundice and in the serum transmitted disease has been established as being between sixty and 150 days.[15] However, mild, subclinical hepatitis without jaundice has been shown experimentally in volunteers by Neefe and associates[21] to recur throughout the fifty to seventy-five days preceding the onset of obvious hepatitis, beginning twelve to thirty-five days after inoculation. Furthermore, Francis[14] has shown that in a case of infectious hepatitis transmitted to the recipient of a transfusion from a donor in the prodromal stage of infectious hepatitis, the incubation period between inoculation and jaundice was only twenty-one days. In volunteers, the serum from this recipient induced jaundice in forty-five days. According to Neefe and associates,[21] the symptoms of the prodromal hepatitis in volunteers included malaise, anorexia, nausea, vomiting, muscular pains, and headache. Examination usually showed slight liver tenderness and occasionally a low-grade fever. These symptoms and signs usually subsided after five days and the interval to the final development of the homologous serum hepatitis was "either asymptomatic or marked by periodic recurrences of mild symptoms and signs." The occurrence of hepatitis without jaundice has also been reported in cases of the post-transfusional type of the disease by Rappaport,[11] and has been observed in cases of infectious hepatitis by Finks and Blumberg.[22] Lichtman[23] has recently stressed this phenomenon and the problems of diagnosis. He points out that a low-grade hepatitis may persist for months or even years unrecognized if jaundice is sought as a symptom. Finks and Blumberg[22] have emphasized that the detection of such cases depends on the obtaining of a history of exposure and also the typical history of the preicteric prodrome. They list anorexia, nausea, vomiting, and abdominal discomfort, especially in the right upper quadrant, as important features of this history. Liver function tests in their group of patients proved valuable in confirming the clinical impression of hepatitis in the face of a normal icteric index. Pollock[24] has shown that cases of infectious hepatitis without overt jaundice or symptom may also occur in epidemics among children. He found that Hunter's test for bilirubinuria was most useful in detecting these conditions. These features are stressed here because they represent the most important clues in the detection of a nonjaundiced but potentially dangerous donor. It is also important to

point out that, as Havens[25] has stressed, little is known as to the length of time that the infective agent is present in the blood or feces of patients either convalescent from or in a clinical relapse of infectious hepatitis.

The pathology of homologous serum hepatitis has recently been reviewed by Wood,[26] who stresses the similarity between this disease and cases of so-called "acute yellow atrophy of unknown etiology." He states that "the burden of proof is on the pathologist to exclude the probability of virus hepatitis, when confronted by a case of so-called idiopathic acute yellow atrophy."

The close relation of homologous serum hepatitis to pediatrics is manifest in the reports of jaundice following the use of prophylactic convalescent serum for measles[27] and for mumps.[28] With the recent account by Loehle[29] of the successful use of oral plasma in newborn and premature infants, the possibility of transmission of infectious hepatitis in this way is raised. Havens[25] transmitted the agent of infectious hepatitis by feeding the serum to volunteers. Furthermore, investigators in England[30] have been able to trace outbreaks of jaundice in diabetic and venereal disease clinics to syringes or needles contaminated with the icterogenic agent, and have suggested that postarsphenamine jaundice is very often in reality homologous serum hepatitis. They have also found cases transmitted through syringes used for intravenous anesthesia as well as several other routine intravenous procedures.

While infectious hepatitis in peace time has been frequent in pediatric age groups, it thus can be seen that the serum transmitted disease must now also be considered in cases of jaundice in children. The occurrence of a fatal case of homologous serum hepatitis in an infant, following transfusions for erythroblastosis fetalis, has prompted this report, to stress that the condition is a pediatric problem as well as a military one, and also to present the pathology of the case.

CASE REPORT

This baby was born Oct. 26, 1945, at the United States Naval Hospital, Oakland, California, with a birth weight of 7 pounds, 13 ounces. The mother was a 28-year-old primipara who had had no transfusions and who had no history of miscarriage. The delivery was normal and except for the necessity of aspirating mucus from the infant's pharynx at the time of delivery, the immediate postnatal course was uncomplicated. On the day after delivery, the infant was noted to be markedly jaundiced, with enlarged liver and spleen. Blood studies at that time revealed a red blood count of 3.5 million and hemoglobin of 14 Gm. (Sahli). The smear showed 95 erythroblasts. The baby, mother, and father were all found to be Rh positive. A titration on the mother's serum by Wiener's method[36] gave no evidence of anti-Rh antibody. The conglutination test[32] was not done. A presumptive diagnosis of erythroblastosis fetalis was made on the assumption that the baby and mother were of different Rh sub-types.

A transfusion of 70 c.c. of whole, citrated, Rh-negative blood was given on October 29, and the baby was followed throughout his hospital stay with red blood counts and hemoglobin determinations. Following the transfusion, the red blood count was 4.3 million, with a hemoglobin of 16 Gm. A smear showed 18 erythroblasts. Five days after birth a smear showed no erythroblasts and none were seen on subsequent smears. The hemoglobin remained up until Nov. 14, 1945, when it was found to be 9.5 Gm. It was thought, however, that the baby would continue to improve with iron supplement, and he was discharged home on November 20 with a weight of 8 pounds, 13 ounces. On discharge, spleen and liver were not palpable.

He did well at home, but two weeks later, when checked in the Outpatient Clinic, he was found to have a hemoglobin of 8.5 Gm. and the red blood count had dropped to 2.65 million. Accordingly, he was readmitted for further transfusions. At the time of admission, liver and spleen were again felt to be enlarged, but the patient otherwise appeared healthy. On December 3, 5, and 8, he was given transfusions from two different donors, a total of 220 c.c. He was discharged from the hospital Dec. 11, 1945, with a hemoglobin of 12.5 Gm. and a red blood count of 4.5 million. He was followed in the Outpatient Department in the ensuing weeks, during which time he showed a good gain in weight and a good appetite.

On Jan. 2, 1946, his hemoglobin was found to be 12 Gm. and his red blood count, 3.75 million. He weighed 12 pounds, 4 ounces. On Feb. 5, 1946, he was brought to the clinic with a complaint of vomiting for two days, with occasional temperature elevations to 102° F. His mother said he had been perfectly well before the onset of these complaints. She said that during these two days his appetite had been very poor and that he had been quite lethargic. Examination at this time was essentially negative. His liver was not noted to be either enlarged or tender. He was treated symptomatically by decreasing his carbohydrate intake and diluting the formula. He returned two days later on Feb. 7, 1946, with the complaint of jaundice, and was again admitted to the hospital.

On admission, the mother gave a history of vomiting for four days prior to admission. Three days prior to admission the mother had noticed a swelling of the left testicle without apparent tenderness. She had noticed a dark yellow color to the urine with staining of the diaper throughout the four days. On the day of admission, about eight hours before coming to the hospital, the mother noted the quite sudden appearance of very yellow color to the skin. She was impressed with the listlessness of the baby. On admission, moderately severe icterus was noted in both skin and sclerae. Over the entire body there were scattered small petechiae. The spleen was enlarged 2 fingerbreadths below the costal margin and was hard and round. The liver was enlarged also to two fingerbreadths below the costal margin. His heart showed a soft, systolic, pulmonic murmur. The left testicle showed a moderately large hydrocele which was tense. The remainder of the physical examination was within normal limits. There was no significant lymphadenopathy. The chest was clear to percussion and auscultation. It was the impression on admission that the baby had an acute hepatitis of unknown etiology. The possibility of late effects of liver damage due to erythroblastosis was considered.

Laboratory findings: red blood count, 3.4 million; hemoglobin, 14 Gm.; white blood count, 9,550, with 2 band cells, 22 segmented cells, 75 lymphocytes, and 1 basophile. There was marked toxic granulation of the polymorphonuclear leucocytes. Urinalysis was normal save for a 4 plus reaction for bile. The icteric index was 71 units. Qualitative Van den Bergh was prompt and direct. Red blood cell fragility (Sanford) was as follows: the patient showed hemolysis, beginning at .40 per cent and complete at .28 per cent; the control began at .44 per cent and was complete at .32 per cent. Kahn test was negative. Cephalin-cholesterol flocculation was 4 plus and blood indices were: packed cell volume, 30; red blood count, 2.9; hemoglobin, 10.5; volume index, 1.03; color index, 107; saturation index, 1.04; mean corpuscular volume, 103.1 cubic microns; mean corpuscular hemoglobin, 36 micromicrograms; mean corpuscular hemoglobin concentration, 35 Gm./100 c.c. packed cells.

Initial treatment consisted of vitamin C and vitamin K parenterally, as well as crude liver extract intramuscularly. On the day after admission, the patient showed a remarkable improvement. There were no new petechiae and the old ones were fading. The jaundice was also thought to be fading. Feedings were well taken and all retained. Bleeding time, which was 15 minutes on admission, was now 5 minutes. He did well throughout this day but at 5:50 A.M., on Feb. 9, 1946, breathing suddenly stopped, with no prodrome of either cyanosis or respiratory distress. The temperature course throughout the hospital stay had ranged between 97° and 100° F. (rectally).

Post-Mortem Examination.—The autopsy was performed by Drs. Melvin Black and David Wood. The body was that of a well-developed, well-nourished, male infant, measuring 67.5 cm. in length. There was no rigor mortis, but lividity of the dependent parts was noted.

The skin showed a few very small petechiae over the cheeks, neck, and the anterior chest. A venipuncture mark was surrounded by a small area of ecchymosis. The conjunctivae were clear and there was no discharge in the nostrils or external ear canals. The thorax showed the usual symmetry and the abdomen was of normal contour. There was no palpable lymphadenopathy. The body cavities were dry. The pleura and peritoneum were smooth and glistening membranes.

Heart: The pericardial cavity contained 25 c.c. of dark yellow fluid. The heart was normal in size and weighed 37 Gm. There were several small hemorrhages at the base of the heart in the subepicardial adipose tissue, lying along the course of the coronary artery. The valves measured as follows: tricuspid, 4.5 cm.; pulmonic, 3.0 cm.; mitral, 3.5 cm.; and aortic, 3.0 cm. The endocardium was smooth and glistening, showing no hemorrhages. The coronary arteries were normally patent. The myocardium was reddish brown in color and fairly firm in consistency, measuring 0.6 cm. in the left ventricle and 0.3 cm. in the right ventricle.

Lungs: The right lung weighed 70 Gm. and the left weighed 55 Gm. They were both of the usual color with light dependent congestion and crepitus throughout. On section, the parenchyma was pinkish tan and without edema. The trachea and bronchi were lined by congested mucous membrane and contained a small amount of mucus. The hilar lymph nodes were small.

Thymus.—The thymus weighed 20 Gm., was triangular in shape, and consisted of the usual dark tan, lobulated parenchyma, in which, however, could be seen several red hemorrhages, averaging 0.3 cm. in diameter. Scattered over the surface of the organ were other hemorrhages, giving it a "flea-bitten" appearance.

Gastrointestinal tract: No abnormalities were noted in the stomach, small intestine, or colon.

Spleen: The spleen weighed 36 Gm. and appeared slightly enlarged, although of normal shape. On section it showed many malpighian corpuscles, which averaged a little over 0.1 cm. in diameter and which were quite prominent.

Liver: The liver was of the usual size, weighing 163 Gm. Its surface was smooth and reddish brown in color, except for the gall bladder area, where there was some postmortem discoloration. Its consistency was quite flabby and on cut section it showed a mottling with very large irregular areas of red alternating with lighter brownish-yellow areas. All these areas showed a prominence of the lobular markings with a grayish-white color to the portal spaces.

Gall bladder: The gall bladder was slightly dilated and contained a very light yellow mucoid bile which was easily expressed into the duodenum. The extrahepatic bile ducts were normal in appearance.

Pancreas: The pancreas was of normal size, shape, and consistency.

Genitourinary tract: Both kidneys were of normal size. The cortices were pinkish-tan in color and the medullae were dark brown and striated. The mucous membrane of the pelves and calyces was bile stained. The bladder was normal and filled with dark yellow urine. The genitals were not remarkable save for a hydrocele around the left testicle which contained about 2 c.c. of clear yellow fluid.

The brain: The brain weighed 725 Gm. and showed the usual contour, gyri, and sulci. The ventricular system was not dilated and there was no abnormal exudate. There was no gross kernicterus.

Microscopic examination.—

Lungs: The bronchi were empty except for small amounts of mucus with scattered, desquamated, epithelial cells. Quite generally, the alveolar and septal walls were considerably thickened due to edema, and there was a moderate, loosely arranged, cellular infiltration by mononuclear phagocytes together with occasional polymorphonuclear leucocytes. There was considerable hyperemia of alveolar and septal blood vessels.

Thymus gland was essentially normal with abundant thymic tissue. There was a mild hyperemia.

Heart: Rather extensive recent hemorrhages were present in the subepicardial adipose tissue. The myocardium was essentially normal.

Spleen: Malpighian bodies were rather large and quite prominent. No necroses were noted in the germinal centers. Moderate numbers of lymphocytes and mononuclear phagocytes diffusely infiltrated the stroma of the intervening pulp.

Pancreas was normal. Islands of Langerhans were numerous and rather prominent.

Brain: Sections of the cerebrum and cerebellum revealed no significant abnormalities. No deposition of bile pigment was noted.

Kidneys and urinary bladder were essentially normal.

Adrenal glands were essentially normal except for a moderate depletion of cortical lipoid.

Testes and epididymis showed moderate hyperemia. Otherwise, sections showed normal infantile structure. There was present no indication of orchitis.

Liver: Various sections taken from different portions of the liver showed a striking subtotal necrosis of liver cells. Those cells which remained possessed an opaque granular cytoplasm in which no nuclear outlines could be seen. Most of the necrotic material had been autolyzed. The sinusoidal architecture was intact. Infiltrating the stroma were moderate numbers of loosely distributed mononuclear phagocytes and lymphocytes. Some of the reticuloendothelial cells of Von Kupffer contained small amounts of yellow pigment.

DISCUSSION

The jaundice and anemia occurring in the first day of life in this case seemed clinically to be typical erythroblastosis fetalis, and it was thought to fall into the 10 per cent of such cases due to Rh sub-group incompatibility. It is obvious, however, that the parity of the mother throws some doubt on this assumption. Unfortunately, opportunity to investigate this matter further did not occur until after the baby's death, at which time blood specimens from the father and mother were obtained. From these it was determined* that the father was Group A Rh positive of the sub-type Rh_o Rh^I Rh^{II}, Hr positive, and that the mother was Group O Rh positive of the sub-type Rh_o Rh^I. The possible incompatibilities in the mother were against either Group A cells or cells containing $Rh.^{II}$ Significant titer of agglutinating antibody to either of these was not demonstrable at this time, which was six months post partum.

The transfusions were all with whole citrated blood obtained from three volunteer donors, all of whom had been on active duty in the Navy for at least twenty-four months and none of whom had been overseas. The blood used was all under five days old. All the equipment involved was autoclaved according to standard hospital procedure. The transfusions were given 101, 66, 64, and 61 days before the onset of symptoms. Any one of these intervals is compatible with the known incubation period of homologous serum jaundice. Following the death of the patient, the donors were questioned very carefully about any illnesses they had had in the last year. None of them had ever had jaundice, nor had any of them been exposed to a known case of infectious hepatitis. Their histories were also negative for virus pneumonia and infectious mononucleosis. None of them had had in the past year any complaints which could be ascribed to infectious hepatitis. It would seem that these three donors represent an example of the unavoidable hazard in the problem of homologous serum hepatitis, i.e., the donor in whom the history is of no support in detecting the presence of hepatitis.

*These examinations were carried out in the laboratory of Dr. L. K. Diamond, Boston, Mass.

The patient in this report showed a very short prodrome of three days during which he had vomiting and lethargy, both of which symptoms have been noted in adults. The sudden appearance of the jaundice is also typical of the adult cases reported. A very detailed questioning of the mother failed to reveal any symptoms during the period after the transfusions which could have been construed as those of latent hepatitis. There was no history of exposure to any known hepatotoxic agent.

The laboratory findings in this case illustrate many of the important features of acute virus hepatitis. The obvious findings of prothrombin deficiency were present on admission and the response to parenteral vitamin K as measured by the bleeding time was dramatic. Bollman and associates have shown[33] that the liver is of great importance in the formation of prothrombin from vitamin K, and they have also demonstrated that, in the presence of severe hepatic damage, prothrombin formation from vitamin K is severely impaired. The response in this patient was not, therefore, typical. Also, in this vein, Kinsey[34] has been able to obtain excellent response to transfusions in patients with hemorrhagic tendency secondary to infectious hepatitis by preparing blood donors in advance with oral vitamin K. The urine and Van den Bergh confirmed the assumption of an obstructive type of jaundice.

The red cell fragility test would seem worthy of special note. Finks and Blumberg[22] showed that an increased resistance of the red cell to hypotonic solutions of saline occurred in cases of infectious hepatitis. Recently, Bohr[35] and Cohen[36] have presented further evidence of this increased resistance. In the present case there was an increase as far as 0.28 per cent saline, which is compatible with the figures reported by the above authors. This feature of infectious hepatitis has received little note in the literature and its occurrence in a case of homologous serum hepatitis is of interest.

The blood indices revealed a slight but definite macrocytic hyperchromic anemia which has been found to occur in cases of infectious hepatitis by Turner and Snavely.[16] Wintrobe and Schumacker[37] have also noted this type of anemia in chronic liver disorders.

The post-mortem findings were typical both grossly and microscopically of fatal cases of either homologous serum hepatitis or infectious hepatitis.[26] The petechiae found in the lungs and thymus would be further evidence of a prothrombin deficiency secondary to the extensive hepatic necrosis. The findings of an acute interstitial pneumonitis could well represent a part of a generalized virus infection as suggested by Wood[26] in discussing a similar finding in a case of fatal epidemic hepatitis.

It would seem pertinent to point out at this time some of the measures which have been suggested for the prevention of homologous serum hepatitis. Of primary importance is the obtaining of a careful and complete history from all blood donors to detect any possible hepatitis either latent or convalescent. This, of course, as illustrated in the present report and, as stressed by Rappaport,[11] will not eliminate the "healthy" carrier or donor in the preicteric phase. The safe interval to allow between hepatitis and the donation of blood has not been

determined with any degree of certainty. MacCallum[38] and Oliphant[39] have showed that the icterogenic agent is not present in the blood two and one-half months after the disappearance of jaundice. Likewise, the detection of a donor in the incubation period of infectious hepatitis seems at present not always possible. It would seem best to refuse any donor who has had infectious hepatitis or jaundice of undetermined origin during the previous six months, at least, and any donor who has received whole blood, plasma, or convalescent serum during the previous six months. Also, some procedure could be developed at blood banks for observation of donors subsequent or even prior to their use. The careful recording of the source of the blood used for a transfusion would facilitate rapid tracing of such donors. Observations of the recipient for at least six months, with determination of serum bilirubin, might yield early diagnosis of homologous serum jaundice and possible expectant treatment. Rappaport[11] has shown that elevation of serum bilirubin extends over a considerable period of time preceding the actual jaundice, although the detection of bilirubinuria would seem to be a more simple routine procedure in the detection of such cases. The successful use of immune globulin prophylactically following transfusions has been reported by Grossman and associates[8] although these authors stressed the fact that failures had also been reported. They advised two injections of globulin, one month apart. This therapy is without effect when given after the onset of homologous serum hepatitis.

The pooling of plasma as a factor has already been mentioned. The use of smaller plasma pools would be much safer than the large pools used in the past and would at least decrease the total number of recipients developing homologous serum hepatitis from a single donor source.

Sodeman,[40] in a recent review, has advised that to insure the removal of the virus agent, contaminated equipment should be sterilized at dry heat, 160° C., for one hour. It would seem evident that rinsing syringes in alcohol would not accomplish this end.

Oliphant[41] has provided evidence that ultraviolet irradiation of icterogenic serum for about ten minutes may inactivate the virus. This, although MacCallum[42] has been unable to repeat these results, might eventually prove of some value.

SUMMARY

1. The clinical and pathologic findings of a fatal case of homologous serum hepatitis in an infant 15 weeks of age are reported. Transmission apparently occurred through the medium of transfusions of whole blood given 60-100 days before onset of the disease. This is believed to be the first report of such a case in this age group.

2. The literature on the subject is reviewed. It is evident that homologous serum hepatitis represents an important hazard in the use of human blood and its derivatives.

3. Means of prevention of such transmission are reviewed.

The author wishes to acknowledge the assistance of Commander David A. Wood, Medical Corps, United States Naval Reserve, and Lieutenant (J.g.) Melvin Black, Medical Corps, United States Naval Reserve.

REFERENCES

1. Paul, J. R., Havens, W. P., Sabin, and A. B., Philip, C. B.: Serum Jaundice and Hepatitis, J. A. M. A. 128: 911, 1945.
2. Epidemic Hepatitis—A War Disease, Bull. U. S. Army Med. Dept. No. 70, page 4, 1943.
3. Circular Letter No. 95, Office of the Surgeon General, Outbreak of Jaundice in the Army, J. A. M. A. 120: 51, 1942.
4. Memorandum Prepared by Medical Officers of the Ministry of Health, Homologous Serum Jaundice, Lancet 1: 83, 1943.
5. Morgan, H. V., and Williamson, D. A.: Jaundice Following Administration of Human Blood Products, Brit. M. J. 1: 750, 1943.
6. Beeson, P. B.: Jaundice Occurring One to Four Months After Transfusion of Blood or Plasma, J. A. M. A. 121: 1332, 1943.
7. Steiner R. E.: Five Cases of Jaundice Following Transfusion of Whole Blood or Human Plasma, Brit. M. J. 1: 110, 1944.
8. Grossman, E. B., Stewart, S. G., and Stokes, Jr., Post-Transfusion Hepatitis, J. A. M. A. 129: 991, 1945.
9. Snell, A. M., Wood, D. A., and Meienberg, L. J.: Infectious Hepatitis With Especial Reference to Its Occurrence in Wounded Men, Gastroenterology 5: 241, 1945.
10. Murphy, H. M.: Transmission of Infectious Hepatitis by Blood Transfusion, Gastroenterology 5: 449, 1945.
11. Rappaport, E. M.: Hepatitis After Transfusions, J. A. M. A. 128: 932, 1945.
12. Grossman, C. M., and Saward, E. W.: Homologous Serum Jaundice Following Administration of Commercial Pooled Plasma, New Eng. J. Med. 234: 181, 1946.
13. Spurling, N., and Vaughn, J.: The Incidence, Incubation Period, and Symptomatology of Homologous Serum Jaundice, Brit. M. J. 1: 409, 1946.
14. Francis, T. Jr., Frisch, A. W., and Quilligan, J. J. Jr.: Demonstration of Infectious Hepatitis Virus in Presymptomatic Period After Transfer by Transfusion, Proc. Soc. Exper. Biol. & Med. 61: 276, 1946.
15. Paul, J. R.: Hepatitis; Clinical and Epidemiological Aspects, Conference on Liver Injury, 1944, Josiah Macy, Jr., Foundation, pp. 75-77, 1944.
16. Turner, R. H., Snavely, J. R., Grossman, E. B., Buchanan, R. N., and Foster, S. O.: Some Clinical Studies of Acute Hepatitis Occurring in Soldiers After Inoculation With Yellow Fever Vaccine, With Especial Consideration of Severe Attacks, Ann. Int. Med. 20: 193, 1944.
17. Havens, W. P.: Experimental Production of Infectious Hepatitis by Feeding Icterogenic Materials, Conference on Liver Injury, 1944, Josiah Macy Jr. Foundation, pp. 77-80, 1944.
18. Lucke, B.: Epidemic Hepatitis, Proc. Inst. Med. Chicago 16: 66, 1946.
19. Neefe, J. R., Stokes, J. Jr., and Gellis, S. S., Homologous Serum Hepatitis and Infectious Hepatitis; Experimental Study of Immunity and Cross Immunity in Volunteers; A Preliminary Report, Am. J. Med. Sc. 210: 561, 1945.
20. Findlay, G. M., and Martin, N. H.: Jaundice Following Yellow Fever Immunization, Lancet 1: 678, 1943.
21. Neefe, J. R., Stokes, Jr., Reinhold, J. G., and Lukens, F. D. W.: Hepatitis Due to Injection of Homologous Blood Products in Human Volunteers, J. Clin. Investigation 23: 836, 1944.
22. Finks, R. H., Blumberg, R. W., Epidemic Hepatitis With and Without Jaundice, Arch. Int. Med. 76: 102, 1945.
23. Lictman, S. S.: Hepatic Insufficiency: Pathophysiology and Clinical Aspects, Ann. Int. Med. 25: 453, 1946.
24. Pollack, M. R.: Missed Cases of Infective Hepatitis, Brit. M. J. 2: 298, 1945.
25. Havens, W. P.: Period of Infectivity of Patients With Experimentally Induced Infectious Hepatitis, J. Exper. Med. 83: 251, 1946.
26. Wood, D. A.: Pathologic Aspects of Acute Epidemic Hepatitis With Especial Reference to Early Stages, Arch. Path. 41: 345, 1946.
27. Propert, A. S.: Hepatitis After Prophylactic Serum, Brit. M. J. 2: 677, 1938.
28. Beeson, P. B., Chesney, G., and McFarlan, A. M., Hepatitis Following Injection of Mumps Convalescent Plasma, Lancet 1: 814, 1944.
29. Loehle, J. R.: Oral Plasma Feeding, J. Pediat. 28: 145, 1946.
30. Memorandum Prepared by the Medical Officers of the Ministry of Health; Role of Syringes in the Transmission of Jaundice, Lancet 2: 116, 1945.
31. Wiener, A. S.: Hemolytic Transfusion Reactions: III Prevention, With Special Reference to the Rh and Cross Match Test, Am. J. Clin. Path. 12: 302, 1942.
32. Wiener, A. S.: Conglutination Test for Rh Sensitization, J. Lab. and Clin. Med. 30: 662, 1945.
33. Bollman, J. L., Butt, H. R., and Snell, A. M.: The Influence of the Liver on the Utilization of Vitamin K, J. A. M. A. 115: 1087, 1940.

34. Kinsey, R. E.: A New Aid in Control of Hemorrhage in Severe Damage to the Liver: Transfusions of Blood Fortified by Administration of Vitamin K to Donors, Arch. Int. Med. 73: 131, 1944.
35. Bohr, D. F.: Erythrocyte Fragility in Acute Infectious Hepatitis, J. Lab. and Clin. Med. 31: 1179, 1946.
36. Cohen, H.: Resistance of Erythrocytes to Hemolysis in Jaundice, Am. J. Clin. Path. 16: 49, 1946.
37. Wintrobe, M. M., and Schumacker, H. S.: The Occurrence of Macrocytic Anemia in Associantion With Disorder of the Liver Together With a Consideration of the Relation of this Anemia to Pernicious Anemia, Bull. Johns Hopkins Hosp. 53: 387, 1933.
38. MacCallum, F. O., and Bauer, D. J.: Homologous Serum Jaundice; Transmission Experiments With Human Volunteers, Lancet 1: 622, 1944.
39. Oliphant, J. W.: Jaundice Following Administration of Human Serum, Bull. New York Acad. Med. 20: 429, 1944.
40. Sodeman, W. A.: Infectious Hepatitis, Am. J. M. Sc. 212: 94, 1946.
41. Oliphant, J. W., and Holloender, A.: Homologous Serum Jaundice; Experimental Inactivation of the Etiologic Agent in Serum by Ultra Violet Irradiation, Pub. Health Rep. 61: 598, 1946.
42. MacCallum, F. O.: Homologous Serum Hepatitis, Proc. Roy. Soc. Med. 39: 655, 1946.

Case Reports

STREPTOMYCIN IN THE TREATMENT OF MILIARY TUBERCULOSIS

GEORGE COBLEY, M.D., AND ELVIRA GOETTSCH, M.D.
LOS ANGELES, CALIF.

STREPTOMYCIN has been shown to be effective in arresting tuberculosis in vitro[1, 2, 3] and in vivo.[4, 5, 6] Waksman and Schatz[3] found *Mycobacterium tuberculosis* to be one of the most sensitive organisms to the bacteriostatic action of streptomycin.

Hinshaw and associates[4] at the Mayo Clinic described the response of twelve patients with generalized hematogenous tuberculosis to streptomycin. In one patient with miliary tuberculosis and no evidence of involvement of the central nervous system, pronounced improvement was noted, both clinically and roentgenographically, after two months of treatment. Six of the eleven patients with central nervous system involvement died; the other five were still living two to ten months after the clinical diagnosis had been established. McDermott[5] observed four patients with hematogenous tuberculosis who were treated with streptomycin. In five weeks all showed almost complete disappearance of roentgen evidence of miliary lesions in the lungs; in one infant, the lungs cleared completely, then meningitis developed late in the course of treatment. At the time of publication it was too early to estimate the final outcome. In infants two cases of tuberculous meningitis were favorably modified by treatment with streptomycin. In one case,[6] the spinal fluid cleared after sixty-eight days of treatment, but deafness persisted; in the other case,[7] a pleocytosis of the cerebrospinal fluid persisted without other abnormality two months after fifty-seven days of treatment.

We feel that the preliminary report of the following case should be made at the present time in order to encourage the treatment of miliary tuberculosis with streptomycin.

CASE REPORT

On Sept. 14, 1946, H. C., an 11-month-old white male infant, was admitted to the Childrens Hospital in Los Angeles with enlarged cervical lymph nodes of six months' duration and fever of two weeks' duration. He had been well and had developed normally until 5 months of age. At that time, a "chest cold" was followed by a hard swelling on the left side of the neck. Four months before admission, tumefactions appeared on the right side of the neck with persisted until hospitalization. During the interim he had had two upper respiratory infections with fever and cough, each lasting about three days. In the three months prior to entry he failed to gain weight, lost appetite, and became more and more listless. One month before admission a skin tuberculin test with 0.10 mg. old tuberculin was found to be negative. Two weeks later the child again developed fever with a wheezing cough and was admitted to another hospital. A second Mantoux test (P.P.D. 0.01 mg.) was placed which showed erythema at the end of twenty-four hours. Because a faint maculopapular rash appeared at this time, the infant was discharged home. A week later he was admitted to the Childrens Hospital.

From the Department of Pediatrics, University of Southern California School of Medicine, and the Childrens Hospital, Los Angeles.

There was no family history of tuberculosis and no evidence of exposure; the mother, father, an aunt and an uncle who reside in the patient's home were found to have normal lungs on roentgen examination. The only possible exposure to tuberculosis, elicited in the history, might have occurred while the patient was visiting in Texas, where he consumed raw milk for six weeks.

On physical examination the baby was chronically ill, listless, and very pale. He was well developed, moderately well nourished, and extremely irritable when disturbed. The musculature was flabby and weakness was so pronounced he could hardly sit up. The temperature was 102.4° F. and the weight was 18 lbs., 11 oz.

The pupils reacted normally to light, the fundi were normal, and no choroid tubercles were noted. The eardrums were normal. The pharynx was acutely inflamed and the tonsils were enlarged and injected. There was visible swelling of the neck without discoloration of the overlying skin. On palpation, the cervical lymph nodes were moderately enlarged (0.5 to 2 cm. in diameter), firm, discrete, and nontender. Respiratory movements were normal in excursion. Slight percussion dullness over the right lung field posteriorly without change in breath sounds was noted; some wheezes and numerous transmitted rhonchi were heard bilaterally on auscultation, but there were no fine râles. The liver edge was palpated 2 cm. below the right costal margin; it was smooth, soft and nontender. The spleen was not felt. The inguinal, axillary and epitrochlear glands were palpable but not enlarged. The neck and spine could be flexed without resistance; the Kernig and Brudzinski tests were negative. Other reflexes were within normal limits.

The hemoglobin was 9.9 Gm. (63 per cent) with a red blood count of 3,960,000. The white blood count was 17,100 with 54 per cent polymorphonuclear leucocytes, 42 per cent lymphocytes, 3 per cent monocytes, and 1 per cent eosinophiles. The sedimentation rate was 27 mm. per hour (Westergren) and the blood Kahn was negative. The cerebrospinal fluid contained no cells, 5 mg. per cent protein, 74 mg. per cent sugar, and 668 mg. per cent chloride. Smears made from the cerebrospinal fluid showed no acid-fast or other bacterial organisms, and the culture was sterile. A smear from the throat was negative for diphtheria bacilli; the nasopharyngeal culture yielded Group A hemolytic streptococci, hemolytic *Staphylococcus aureus,* and several nonpathogens. The urine was negative. The skin tuberculin test to 0.01 mg. of old tuberculin was negative, but when an increased dose of 0.1 mg. was applied, an area of erythema and induration 1 cm. in diameter developed. A roentgenogram of the chest showed a diffuse hematogenous spread of millet-sized lesions in both lung fields, which was interpreted to be consistent with miliary tuberculosis.

A biopsy of a cervical lymph node was done to provide proof of the diagnosis of tuberculosis. A smear of the excised gland showed characteristic acid-fast bacilli; microscopic examination showed caseous material with whorls of epithelioid cells and interlacing bundles of young fibrous tissue. An occasional Langhan's type of giant cell was noted within the whorls of epithelioid cells. The normal lymph node structure was completely destroyed. A diagnosis of tuberculosis of a cervical lymph node was made.

Streptomycin was started on the fifth hospital day; a dose of 0.125 Gm. was given intramuscularly every three hours (one gram a day) for the next three months. A high caloric, vitamin-enriched diet was offered and several transfusions were given to combat the moderate anemia.

During the first five days in the hospital, the fever fluctuated around 102° F.; thereafter, the temperature remained normal throughout the course of hospitalization, except for several transient elevations associated with mild upper respiratory infections. The fact that the temperature became normal

Fig. 1.—*A*, X-ray of chest before therapy. Note the diffuse spread of millet-sized lesions in both lung fields. *B*, One month after the completion of streptomycin therapy. The miliary lesions which had disappeared seven weeks after initiation of treatment have not recurred.

within twenty-four hours after streptomycin was instituted is probably a coincidence. Four days after streptomycin was started the lungs were clear to percussion and auscultation. The biopsy wound healed quickly and the swelling of the lymph nodes receded at an amazing rate. One month after treatment with streptomycin was initiated, the weight had fallen to 17 lbs., 10 oz., a loss of one pound. The erythrocyte sedimentation rate was maintained at essentially 33 mm. in one hour (Westergren). Serial roentgenograms of the lungs showed practically no change.

Five weeks after treatment was started the cervical lymph nodes had regressed until they were barely palpable. During the second month of treatment the patient gained 20 oz. of weight; the erythrocyte sedimentation rate rose to 57 mm. per hour (Westergren), which was attributed to the inflammatory reaction at the sites of injection of streptomycin. Isolation during the first six weeks of hospitalization was obligatory, and it was felt that the unavoidable lack of attention and the loneliness were presumably responsible for anorexia and a failure to gain weight. Serial roentgenograms of the lungs were taken weekly and it was not until the seventh week after therapy was started that marked improvement was noted.

During the third month of treatment the sedimentation rate remained elevated but roentgenographic improvement of the lungs continued. Toward the last it became exceedingly difficult to find sites for the injection of the streptomycin, as the most favorable muscular areas were indurated and inflamed. After three months of treatment it was necessary to discontinue the drug because of this factor.

For one month after cessation of the drug the patient remained afebrile and began to gain weight. The sedimentation rate fell to 13 mm. per hour (Westergren) and remained at this level for the last three weeks of hospitalization. At the time of discharge on Jan. 22, 1947, the weight was 19 lbs., 1 oz. The blood count, urinalysis, and cerebrospinal fluid were all within normal limits. As shown in Fig. 1 the miliary lesions in the lung fields, which had disappeared seven weeks after initiation of treatment, had not recurred at the time of discharge from the hospital.

COMMENT

Clinical evidence has shown that streptomycin has a palliative effect in patients with miliary tuberculosis. No complete eradication has yet been reported. It is too early to determine the final result in our patient, since a longer period of observation will be necessary.

The minimum dosage and the length of adequate treatment must still be accurately determined. Early diagnosis is helpful and persistent treatment with maximal doses should be maintained in cases of miliary tuberculosis, at least for three months. Intrathecal treatment has been recommended in cases in which the central nervous system is involved.

Toxic manifestations have been reported in the majority of patients receiving prolonged treatment with streptomycin. In our case the only definite untoward effect was the local reaction at the sites of injection. No evidence of disturbance of equilibrium or hearing could be detected by clinical observation. A Kobrak caloric test revealed no response to horizontal and vertical canal stimulation in either ear. Although the evidence of possible damage to the vestibular end organs seems conclusive at the present time, final interpretation should be reserved until more extensive studies with the test in this age group have been done.

SUMMARY

1. The clinical features of a case of miliary tuberculosis treated successfully with streptomycin have been described. The diagnosis of tuberculosis was confirmed by biopsy of a cervical lymph gland.

2. A total dosage of 91 Gm. of streptomycin was given; one gram daily in divided amounts for three months.

3. Marked improvement both clinically and roentgenographically was obtained. No relapse has occurred within two months after cessation of the treatment.

REFERENCES

1. Feldman, W. H., Hinshaw, H. C., and Mann, F. C.: Streptomycin in Experimental Tuberculosis, Am. Rev. Tubere. 52: 269, 1945.
2. Youmans, G. P., and McCarter, J. C.: Streptomycin in Experimental Tuberculosis Var. Hominis, Am. Rev. Tubere. 52: 432, 1945.
3. Waksman, S. A., and Schatz, A.: J. Am. Pharm. A. (Scient. Ed.) 34: 273, 1945.
4. Hinshaw, H. C., Feldman, W. H., and Pfuetze, K. H.: Treatment of Tuberculosis With Streptomycin, J. A. M. A. 132: 778, 1946.
5. Keefer, C. S. et al. (The Committee of Chemotherapeutics and Other Agents of the National Research Council), Streptomycin in the Treatment of Infections, J. A. M. A. 132: 70, 1946.
6. Cooke, R. E., Dunphy, D. L., and Blake, F. G.: Streptomycin in Tuberculous Meningitis: A Report of Its Use in a One-year-old Infant, Yale J. Biol. & Med. 18: 221, 1946.
7. Krafchik, L. L.: Tuberculous Meningitis Treated With Streptomycin, J. A. M. A. 132: 375, 1946.

CHOLECYSTITIS AND CHOLELITHIASIS IN A CONGENITAL DIVERTICULUM OF THE GALL BLADDER IN A THREE-YEAR-OLD BOY

FRANCES H. BOGATKO, M.D., AND JULIA MEHLMAN, M.D.
NEW YORK, N. Y.

DUPLICATION of the gall bladder is a rare anomaly and is reported by Boyden,[1] Bryan,[2] and other investigators as occurring once in 3,000 to 4,000 cases. On embryologic and anatomic grounds, double gall bladder is classified as follows: (1) ductular, with two cavities and two cystic ducts; (2) bilobular, with two cavities and one cystic duct; (3) diverticular, with one large cavity communicating with one or more small cavities; and (4) trabecular. The anomaly is first discovered at operation or autopsy. Golob and Kantor[3] point out that if cholecystography is performed, it must be remembered that since a diseased gall bladder may coexist with a normal accessory gall bladder, the former may not be visualized while the latter would reveal a normal sequence; this finding might easily lead to a wrong negative diagnosis with the result that an unsuspected active lesion might be overlooked.

CASE REPORT

On May 29, 1945, D. W., a 3-year-old boy, was admitted to the New York Infirmary with a history of jaundice and anorexia for seven weeks previous to admission. Two months before admission (March, 1945), this patient had an upper respiratory infection associated with severe abdominal pain around the umbilicus, vomiting, and low-grade fever. He had been seen at this time by two physicians who excluded appendicitis and made a diagnosis of intestinal influenza. Three grams of sulfadiazine were given over a period of two days. One week after the onset of illness, jaundice developed gradually. At this time there was no nausea, vomiting, diarrhea, or itching of skin, but the occasional slight rise in temperature continued. Before admission to the hospital, the mother observed that the stools were becoming clay colored. There was no history of improper diet, gastritis, or food poisoning in the family or neighborhood.

The family history was irrelevant. The child had had jaundice at 1 year of age for three weeks during dentition. On admission, physical examination showed an undernourished, chronically ill child, with markedly icteric skin and sclerae. Abdominal examination revealed an enlarged, smooth, tender liver which extended 4 fingerbreadths below the right costal margin. The spleen was palpable below the left costal margin. Otherwise, the abdominal examination was reported negative. On admission, the temperature was 100.2° F. pulse 130, and respirations 52.

The urine showed a trace of albumin, a few hyaline casts, and the presence of bile. Other laboratory tests were as follows: hemoglobin, 70 per cent; adult polymorphonuclear cells, 47 per cent; red blood cells, 3,500,000; immature polymorphonuclear cells, 2 per cent; white blood cells, 12,200; lymphocytes, 32 per cent; eosinophiles, 19 per cent. The blood type was Group A: The Rh factor was negative. The blood Wassermann was negative. Blood serum was negative for *Bacillus abortus* and *Bacillus typhosa*. The sedimentation test showed a sedimentation index of 0.6. A tentative diagnosis of toxic or infectious jaundice or acute hepatitis was made.

Studies of liver function were made. There was an immediate, direct, van den Bergh reaction. The icteric index was 37.5. Cholesterol was 518. The fragility test was within normal limits. Examination of the feces showed the presence of neutral fats and fatty acids but was negative for ova and parasites. Roentgenographic examination of the abdomen showed an enlarged liver but no other abnormalities. Roentgenographic examination of the lungs showed no evidence of disease.

Five per cent glucose was given intravenously, and penicillin intraumuscularly without any appreciable improvement. Solu B was also given orally. An unsuccessful attempt was made to drain the duodenum. The child was observed over a period of about four weeks, during which time the icteric index ranged from 37.5 to 55. The temperature ranged from 98° to 103° F. The child had a variable appetite, was apathetic, and had recurrent attacks of colicky pain not localized to any point. The jaundice subsided and then became deeper again. On June 26th a surgical consultation was held, and a tentative diagnosis of a pancreatic cyst was made. At this time, there was a definite cystic mass about 4 cm. in diameter palpated at the liver margin. On July 12, 1945, roentgenologic examination of the gastrointestinal tract showed a normal stomach and duodenal bulb, with a suggestion of narrowing of the upper portion of the second part of the duodenum. This appearance was consistent with a pancreatic cyst or congenital band crossing the duodenum, but was definitely not considered obstructive. The diagnosis was duodenal abnormality, probably extrinsic.

The day after the gastrointestinal x-rays, the child had a sudden attack of pain while eating, at 5:30 P.M. On abdominal examination, a tense, round, tender mass about 4 cm. in diameter could be seen and easily palpated in the gall bladder region. This attack was typical of gall bladder colic, and was quickly relieved by hypodermic administration of atropin. At this time, the white blood count was 15,950 with a differential of 68 per cent polymorphonuclear cells, and 3 per cent immature polymorphonuclear cells. A diagnosis of cholelithiasis was made and a laparotomy advised for obstructive jaundice. On July 18, the cholesterol was 556 and the cholesterol esters 159. At operation, on July 19, the liver was found to be the seat of chronic congestive cirrhosis; the gall bladder had a thickened wall and was firmly adherent to the duodenum and the surrounding structures. After dissection in the area of the ampulla, an egg-shaped protrusion suggesting a diverticulum was found. The common duct was then identified, opened, and explored. A probe passed readily through the papilla of Vater and into the right and left hepatic and common hepatic ducts. No stones were found. The common duct was drained by means of a T tube. Because of the very serious condition of the child, it was thought advisable to do as little surgery as possible. It was thought that he would not stand the removal of the gall bladder after ascertaining where the diverticulum arose. There were numerous adhesions in this region; therefore, a choleystostomy was done and a tube inserted into the gall bladder with double inversion of the gall bladder wall. Biopsy of the gall bladder was taken for microscopic examination. It was assumed at this time that the child's jaundice was due to either an inflammatory condition of the gall bladder or of the diverticulum, or a pressure phenomenon from the diverticulum, which lay very closely associated and adherent to the duodenum. Pressure of this diverticulum would also account for the contracture noted in the duodenum, in radiologic studies.

The pathologic diagnosis was "gall bladder tissue with marked hyperplasia of mucous membrane (papilloma)."

The postoperative course was uneventful. On July 23, 1945 (fourth postoperative day), a barium meal was given and x-rays of the duodenum and biliary tract taken. Later, on July 30, 1945, diodrast was injected into both drainage tubes (common duct and gall bladder). This showed narrowing of the second portion of the duodenum as before, and a ready connection between the common duct, hepatic duct, and both drainage tubes, with questionable filling of the gall bladder. On August 16, about four weeks after the first operation, it was considered advisable to re-explore the child. The operator was not certain that the diverticulum was of the gall bladder, but felt that it must be, as radiologically there was no evidence of a diverticulum of the duodenum. It was believed, however, that the primary operation had not eliminated the cause of the prolonged jaundice and abdominal pain. Therefore, a cholecystectomy was decided upon. On opening the wound, the cholecystostomy tube went into one branch of the biped organ. The second branch, which was markedly bound down, proved to be the other branch of the diverticulum. It was adherent to the duodenum and was about 4 by 3 cm. in diameter. The wall was quite thickened. Both of these organs came together just above the cystic duct so that it was possible to remove them with exposure of the cystic duct and ligation thereof. The gall bladder was removed and contained some biliary gravel. The pathologic report was as follows: "Gall bladder with two sacs connected by a small passageway about 1 cm. in diameter. This is probably a congenital malformation with double sac and possible infolding of liver tissue attached."

The child had a satisfactory convalescence, and about four weeks after the second operation, was discharged in good condition. On discharge, his icteric index was 6.2 and the hemoglobin was 80 per cent with a white blood count of 8,000. He was seen June 18, 1946. He had gained 10 lb. and had no complaints.

REFERENCES

1. Boyden, E. A.: The Phyrigian Cap in Cholecystography; a Congenital Anomaly of the Gall Bladder, Am. J. Roentgenol. 33: 589, 1935.
2. Bryan, L.: Double Gall Bladder, Radiology 35: 242, 1940.
3. Golob, M., and Kantor, J. L.: Double Gall Bladder: Two Cases, Am. J. Digest. Dis. 9: 120, 1942.
4. Walters, W., and Snell, A. M.: Diseases of the Gall Bladder and Bile Ducts, Philadelphia, 1940, W. B. Saunders Company, pp. 33-34.

PERIARTERITIS NODOSA IN CHILDHOOD

ELIZABETH J. BRADLEY, M.D.
SAN FRANCISCO, CALIF.

SINCE Kussmaul and Maier described periarteritis nodosa in 1866, many other cases have been reported, especially in recent years, but most of these have been in adults. In children the disease is unusual. Keith and Baggenstoss[1] state that from 1866 to 1932, a period of sixty-seven years, only twenty-three childhood cases were reported, and from 1933 to 1939, a period of only seven years, twenty-one cases. A clinical diagnosis during life was made in only seven, or 15 per cent, of these cases. Rothstein and Welt,[2] in 1933, reported that of 195 proved cases recorded up to that time, twenty-three, or 11.8 per cent, occurred during infancy and childhood, with a ratio of approximately four males to one female, and a fatality rate of 90 to 95 per cent.

CASE REPORT

D. D., a 10-year-old Filipino boy, entered the San Francisco City and County Hospital Nov. 6, 1944. Three weeks before entry he had had a severe sore throat and two weeks later complained of a sore neck, joint pains, and vomiting. Four days before entry he began to have severe abdominal pain in his right lower quadrant which was cramplike in character and became progressively worse. He had been treated by a private physician with "white pills" given every three hours. We were unable to determine whether or not these were sulfonamide tablets. He had had frequent bouts of epistaxis before the present illness, the last being a day before admission to the hospital. Two days before entry he had urinated only a few drops in twenty-four hours. For about one year he had complained of pains in the back of his legs and in the last three months had lost 8 to 10 lbs.

His past history included an entry into San Francisco City and County Hospital on Aug. 8, 1936, at the age of 21 months, for bilateral otitis media. A myringotomy was performed with uneventful recovery. His next hospital stay was at the same hospital on April 4, 1941, at the age of 6½ years for depressed skull fracture. He received sulfanilamide crystals in the wound at this time. His recovery again was uneventful. He had been seen at Stanford University Children's Clinic on four occasions for tonsillitis. His birth and development were normal. Cod liver oil and orange juice had been taken in adequate amounts. He had had measles, varicella, and pertussis, but not rheumatic fever. There was complaint of phimosis with some pain on urination for over one year.

Physical examination on entry revealed a thin boy of about the stated age complaining bitterly of abdominal pain. Temperature was 100.6° F., pulse 88, respiration 18, and blood pressure 145/115. The skin showed no lesions. There was no edema about the eyes, and the pupils reacted to light. The fundi showed no hemorrhage or exudate, and the discs were normal. The ears and throat were not red and the trachea was in the midline. There were large, tender, anterior, cervical lymph nodes and small posterior cervical nodes; the axillary, inguinal, and epitrochlear nodes could not be felt. The lungs were clear to auscultation and percussion. The heart rate was 88, the rhythm regular, and no murmurs or rub were heard. The abdomen was not distended, there were no herniae,

From the Department of Pediatrics of the Stanford University School of Medicine.
Material available through the Department of Public Health, J. C. Geiger, M.D., director.

and the liver and spleen were not palpable. There was definite right lower quadrant tenderness with guarding. No costovertebral angle tenderness was elicited. Moderate phimosis was present. The extremities showed no edema or wasting, and the reflexes were normal. Laboratory results were as follows:

Tuberculin 0.1 mg. intracutaneous was negative in twenty-four and forty-eight hours.

Blood: Nov. 6, 1944, hemoglobin was 13 Gm. per cent; red blood cells, 4 million; white blood cells 22,000, with 85 per cent polymorphonuclears and 15 per cent lymphocytes.

Urine: Nov. 6, 1944, the voided specimen was of amber color, and turbid with a pH 5.5, albumin 4+, sugar negative, and acetone negative. The sediment was granular casts 1 per high dry field, hyaline casts 2 per high dry field, broad casts 1 per high dry field, 3 blood cell casts, 50 to 70 white blood cells per high dry field and 50 to 70 red blood cells per high dry field.

Blood: Nov. 18, 1944, the hemoglobin was 8 Gm. per cent, white blood cells 36,000.

Urine: Nov. 8, 1944, showed no change from Nov. 6, 1944. Nov. 14, 1944, albumin 3+, pH 5, specific gravity 1,000. Sediment showed hyaline casts 1 per high dry field, granular casts 1 per high dry field, white blood cells 20 per high dry field, red blood cells 10 per high dry field. No other elements were present.

Blood: Nov. 25, 1944, the hemoglobin was 4 Gm. per cent, red blood cells 1.4 million, white blood cells 30,000, with 88 per cent polymorphonuclears, no eosinophiles, 8 per cent lymphocytes, and 4 per cent monocytes.

Urine: Nov. 23, 1944, it was grossly bloody with a specific gravity of 1.008, albumin 2+, pH 5.8. Sediment showed white blood cells 75 per high dry field, a few hyaline and granular casts, red blood cells 100 to 150 per high dry field.

(No Addis count could be done accurately because the specific gravity was not over 1.010 when there was a measurable amount of urine.)

Blood: Nov. 10, 1944, blood urea, 363 mg. per cent; Nov. 10, 1944, blood serum creatinine, 4.7 mg. per cent; Nov. 14, 1944, blood urea, 227 mg. per cent; Nov. 16, 1944, serum proteins, 5.8 Gm. per cent; Nov. 18, 1944, blood urea, 339 mg. per cent; Nov. 20, 1944, blood urea, 128 mg. per cent.

The diagnostic impression on entry was acute glomerulonephritis or periarteritis nodosa.

Course.—The patient had a severe nosebleed the second hospital day and continued to complain of abdominal pain. Because of oliguria he was given fluids by vein, mainly 10 per cent dextrose in distilled water. Five days after entry he began to show definite periorbital edema as well as edema of the legs and genitalia. He vomited about 150 c.c. of bright red blood. Râles were heard in the lower left lung field. By this time he no longer had oliguria. The next day penicillin, 15,000 units every three hours, was begun and continued for nine days without benefit. The surgical opinion on the eighth hospital day, obtained because of abdominal distention and severe generalized abdominal pain, was that he had partial ileus with edema of the peritoneum and bowel as well as free fluid in the abdomen. On the fourteenth hospital day, he had difficulty in breathing and was found to have a pulse of 105, blood pressure of 150/100, with dullness to percussion, moist râles, and diminished breath sounds at both lung bases. Since he had signs of cardiac failure, he was given cedilanid in appropriate doses and seemed better the next day. On the nineteenth hospital day he had signs of peritonitis with rebound tenderness, and only slight peristalsis. He was given a transfusion of 500 c.c. of whole blood slowly but continued to go progressively downhill. A muscle biopsy was scheduled but the patient died on November 29, before this could be performed.

*Autopsy.**—The kidneys were swollen and blotchily hyperemic. In the paler areas, innumerable, minute, punctate hemorrhages could be seen covering the surfaces uniformly. On the cut surface there were a few tiny foci of opaque yellowish deposits suggestive of fat. No infarcts could be found but a few of the interlobular vessels here and there were plugged with dark red or paler clots or thrombi. The lining of the pelves, ureters and bladder was edematous and contained scattered tiny hemorrhages. These were more numerous in the bladder where an occasional larger mucosal hemorrhage occurred. There was no evidence of lower urinary obstruction or infection. The lungs and other tissues were very edematous. The heart was hypertrophied and pale. There was no valvular disease except for a tiny fibrous excrescence on the posterior mitral leaflet. There were a few yellow intimal streaks in the root of the aorta. There were no coronary artery or pericardial lesions. The pancreas was normal. The spleen was large and the Malpighian bodies very prominent, but there were no infarcts. The liver was pale and swollen and the lobular markings indistinct. There were many scattered, sharply circumscribed dark patches at the capsular surface. These measured from 10 to 5 mm. or more in greatest dimension. They were often visible through the capsule as slightly sunken darker areas. Their cut surface showed tiny periportal deposits with broad dark central zones. These were apparently infarcts of the liver. The gall bladder wall was thickened, the lining was pale, pinkish and contained numerous punctate hemorrhages, but there was no ulceration. There were several small, superficial bile-stained ulcers of the jejunal mucosa but no serosal or gross vascular lesions. The mesenteric lymph nodes were large and pale. No mesenteric vascular lesions were seen.

Histological Examination.—On the adrenals there was slight to moderate patchy depletion of cortical lipoid, but in many places the cortical and medullary cells were normal. However, numerous small vessels, the type of which could not be identified, mostly located near the periphery of the cortex, showed conversion of the wall into a hyaline, strongly eosinophilic, layer which fused with similar eosinophilic material in the lumen which sometimes was completely filled with this substance. There were polymorphonuclear leucocytes and fragmented nuclei in the vessel walls, and around them there were frequently accumulated lymphoid cells, polymorphonuclear leucocytes, and large cells resembling fibroblasts. Only occasional eosinophiles were seen. The pericapsular tissue was thickened in places by cellular fibrous tissue and several larger vessels, some definitely arteries, showed changes like those within the adrenal substance.

Pathologic lesions similar to those described in the adrenal were noted in the heart, diaphragm, liver, kidney, skeletal muscle, intestine, and gall bladder.

COMMENT

This was a classical case of so-called periarteritis nodosa, which showed unusually extensive lesions. The appearance of some of the involved vessels suggested that they might be veins, although so much destruction had occurred that positive identification was impossible. No bacteria could be identified in the lesions.

The interesting features of the present case are: The onset about three weeks after an acute sore throat; the possible relation to sulfonamide therapy in a patient who had had previous treatments with the same type of drug; the fact that the correct diagnosis was suspected at entry on the basis of the clinical data, and confirmed by the characteristic urinary sediment, and without biopsy.

*Material on the autopsy made available by the Department of Pathology of the Stanford University School of Medicine. The macroscopic description was by Dr. William Carnes, the histological by Dr. Alvin J. Cox, Jr.

The "telescopic urine sediment," which appears to be a characteristic of the group of vascular inflammatory diseases (angiitis) to which periarteritis nodosa belongs, and which are so difficult to diagnose during life, is a valuable diagnostic aid that deserves wider recognition.

Krupp[3] has made important observations on the value of urinalysis in establishing a diagnosis. He reported that fourteen out of twenty-one patients with visceral angiitis had specific urinary findings. In our own case it was the urinary sediment that suggested periarteritis. Krupp included under the heading of visceral angiitis, lupus erythematosus and Libman-Sachs Disease, as well as periarteritis nodosa. He pointed out, however, that the similarity in urinary sediment did not necessarily imply a common etiological agent in these three conditions. According to Krupp, the urinary sediment in visceral angiitis shows simultaneously the changes found in all three stages (Addis classification) of glomerulonephritis; this is the so-called "telescopic sediment." Thus one may find red blood cells, white blood cells, red blood cell casts, oval fat bodies, granular casts, hyaline casts, and broad casts in a single urinary sediment from these patients, accompanied by large amounts of protein. It is of interest that 80 per cent of patients with periarteritis nodosa show definite renal changes.

SUMMARY

A case of periarteritis nodosa with necropsy, in a 10-year-old boy is reported.

REFERENCES

1. Keith, H. M., and Baggenstoss, A. H.: Primary Arteritis (Periarteritis Nodosa) Among Children, J. PEDIAT. **18**: 494, 1941.
2. Rothstein, S. L., and Welt, S.: Periarteritis Nodosa in Infancy and in Childhood, Am. J. Dis. Child. **45**: 1276, 1933.
3. Krupp, M. A.: Urinary Sediment in Visceral Angiitis (Periarteritis Nodosa Lupus Erythematosus, Libman-Sachs "Disease"), Arch. Int. Med. **71**: 54, 1943.

Medical Care

THE TREATMENT OF ACUTE POLIOMYELITIS TOGETHER WITH SOME SUGGESTIONS ON DIAGNOSIS

PHILIP M. STIMSON, M.D.*
NEW YORK, N. Y.

WHEN confronted with acute poliomyelitis, especially if the patient is seriously ill, many doctors are very much at a loss to know how best to care for the afflicted child. The purpose of this paper is to clarify and enumerate, in their order, steps that might be taken.

The first thing to be done is to comfort and reassure the patient and his family and to seek to obtain their cooperation and confidence. A panicky person is naturally tense, and increased muscle tension being an important factor in practically every case of the acute disease, many patients aggravate their symptoms by their nervousness. This is particularly true of patients with the more serious manifestations, those of bulbar and respiratory difficulty. It is highly important that, from the beginning, the patient be helped to be as composed and relaxed as possible.

The next step is to determine the indications for immediate treatment, and, in particular, to determine if there are evidences that the patient's life may be at stake. The great majority of early deaths in poliomyelitis are due to failure of either the cardiac or the respiratory centers in the medulla or bulb. The bulb also contains the nuclei of the ninth, tenth, eleventh, and twelfth cranial nerves. Hence, when there is evidence of involvement of one or more of these nerves, one must be prepared for weakness or even failure of one or both of the two vital centers. A failing cardiac center is revealed by a rapid, thready irregular pulse and a falling blood pressure. When the respiratory center is failing, the patient's breathing is apt to be irregular and shallow, but if there is no other cause for breathing difficulty, he can, on demand, take a deep breath.

Because the functions of the ninth to twelfth nerves overlap to a considerable extent, it is customary to determine not which nerve is involved but what so-called bulbar manifestations are present. These include such evidences of weakness of the soft palate as regurgitation of fluids through the nose, loss of the gag reflex, and blurring of the speech. The tongue may show weakness by deviating to one side or the other. Because of weakness of the lateral pharyngeal muscles there may be difficulty or inability to swallow. Inability to cough is commonly also present in bulbar cases because of an inability to close the glottis. The combined lack of coughing and swallowing allows mucus and saliva to accumulate in the pharynx and act as a mechanical barrier to the passage of air to the lungs. Unless this fluid is continuously removed, the patient "drowns" in his own secretions.

*Associate Professor of Clinical Pediatrics, Cornell University Medical College.
From the Poliomyelitis Division of the Knickerbocker Hospital.

Hence, when a patient is recognized as being a bulbar case, with imperiled cardiac and respiratory centers and with loss of ability to swallow, his two great needs are that the condition of the pulse and blood pressure be closely watched and controlled, and that the pharynx be kept clear of accumulations of mucus. These patients are apt to be very restless and yet they should have quiet and rest; hence, skillful nursing care is of the utmost importance. The old adage: "If you don't know what to do, do nothing," holds true. Wrong treatment does more harm than no treatment. It is obvious, however, that the mucus must be removed. The foot of the bed is raised to obtain postural drainage, and the patient is placed either on his side or his abdomen. Repeated, gentle suction is usually necessary, and if there is much mucus seeping into the trachea or forming there, suction through a laryngoscope or a bronchoscope may be necessary. Even a tracheotomy to by-pass the mucus and to enable repeated suction through the tracheotomy tube has been considered lifesaving in some clinics.

To support the bulbar centers, the early use of oxygen is very beneficial. Because oxygen tents and masks make it very difficult to keep the pharynx clear of mucus, it is best given by nasal catheter, a procedure which, if skillfully done, is of slight, if any, discomfort to the patient. The oxygen should first pass through a watertrap, then through a soft rubber catheter, which, after being lubricated, is gently inserted in the patient's nostril a distance one and a half inches less than the distance from the nostril to the external auditory meatus, in the adult. This distance is previously measured along the patient's cheek and in children is about a half inch shorter than in adults. The oxygen should be flowing gently through the catheter at the time of insertion, and after installation the rubber tubing should be bent straight up to the forehead and fastened there with adhesive, rather than laterally to the cheek, the former position being much more comfortable for the patient. When the catheter is comfortably in place, the flow of oxygen is then increased to an amount sufficient to prevent cyanosis, usually from 4 to 6 L. per minute.

Of drugs intended for bulbar stimulation, the best is caffein, which should be given in doses of 10 mg. of the sodium citrate per kilogram of bodyweight, either subcutaneously or intravenously, and repeated every one-half hour if necessary. For falling blood pressure, neosynephrine by hypodermic in doses of $\frac{1}{10}$ mg. per kilogram may be of additional assistance.

Difficulty in swallowing should be respected and nothing should be given by mouth lest the food or fluid be aspirated by accident into the trachea. However, the patient's fluid intake must be preserved, and intravenous fluids are given. A hypertonic solution of 10 per cent glucose is given first in the hope of reducing edema of the central nervous system, from 500 to 1,000 c.c. being given to an adult. This is followed by enough 5 per cent glucose, some in saline solution, to give the average adult an intake of perhaps 2 L. of fluid a day. More seems to increase the tendency of the pharynx to be flooded with mucus and saliva.

When the inability to swallow persists more than two or three days, it is well to try to pass a well-lubricated Levine tube through a nostril down into the

stomach. If the attempt makes the patient gag, and vomiting is threatened, it should be stopped at once, because vomiting is a very dangerous complication for patients who can neither cough nor swallow. But if the tube can be passed successfully, fluid nourishment can be introduced directly into the stomach by means of the tube and the patient should be fed such preparations as egg milk shakes fortified with vitamins and amino acids. The tube can be left in place a number of hours but may be withdrawn at night so that the patient may sleep more comfortably. Poliomyelitis patients have been thus tube-fed for two weeks or more, but usually the ability to swallow begins to return in about a week. When the patient can swallow his own saliva, sips of water may be tried, followed by sweetened fruit juices and later by more substantial but easily swallowed nourishment such as broths, gelatins, applesauce, and possibly Junket. Milk, as such, should be given sparingly, if at all, the first few days of swallowing. It sticks with the mucus in the pharynx and also is readily vomited.

With or without evidences of bulbar involvement, there may be difficulties of breathing because of either weakness or tightness of the muscles used in breathing, or both. While there are many primary and secondary muscles used in the act of respiration, the essential ones are the intercostals and the diaphragm. Because of the proximity of the nuclei of their nerves of innervation in the cervical cord, there is a close relationship between weakness of the deltoids and of the diaphragm; in fact, when both deltoids are paralyzed, there is almost always marked weakness of the diaphragm. Hence, if both deltoids fail, a very careful watch should be kept of the diaphragm. In normal breathing, the diaphragm descends with inspiration and the anterior abdominal wall bulges out. But when the diaphragm is paralyzed, which may be the case on only one or on both sides, it rises into the thorax on inspiration. Observation with a fluoroscope may be necessary to detect this reversed motion, but sometimes it can be determined by careful inspection.

The clinical picture is further complicated by the fact that when the intercostals and the diaphragm are weak, they are also usually tight, this tension in itself adding materially to the dyspnea or difficulty of breathing. When the diaphragm is tense, expiration is difficult; when the intercostals are tight, inspiration is difficult; and when both are involved, the chest seems almost immobile. Furthermore, tightness lower down in the body, involving the muscles of the anterior abdominal wall, may so pin down the thoracic cage as to interfere greatly with the act of breathing.

Thus many factors may singly or together contribute to respiratory difficulty in poliomyelitis, and treatment will depend on which factors are the predominating cause in any particular case. The respiratory center in the medulla may be failing; mucus may be obstructing the passage of air to the lungs; the tiny abductors of the vocal cords may be weak, allowing the cords to come together and close the glottis; the intercostals and the diaphragm may be weak; they or other muscles may be too tight; and, finally, the patient may be too panicky to try to breathe.

Certain principles control the choice of treatment procedures. Bulbar patients almost always do badly in respirators. Oxygen must have a reasonably

clear passageway to the lungs. Tight muscles can be relaxed appreciably and often rapidly by hot, moist heat. The patient usually can be led to cooperate. And finally, if the patient hasn't enough muscle power to inhale and exhale, he must have artificial respiration.

Hence, when bulbar manifestations predominate in the breathing difficulty, the initial treatment is as just described for other bulbar cases, using oxygen, postural drainage, suction, and caffein. Where these measures are not sufficient and the patient is showing increasing difficulty in obtaining sufficient oxygen, tracheotomy done under local anesthesia may prove lifesaving by providing a by-pass for oxygen to the lungs, especially when the vocal cords are relaxed together or when there is much mucus in the trachea. Suction through the tracheotomy tube, especially if combined with gentle irrigation with a sterile sodium bicarbonate solution, can be used to keep the trachea clear. Then, moistened oxygen can be fed gently to the tracheotomy tube through a four-way connecting tube which permits oxygen to enter the trachea during inspiration, and, during expiration, to pass through a water bottle, which offers just enough resistance during inspiration to prevent the escape of oxygen by this passageway. This use of tracheotomy tube and oxygen was employed extensively and with considerable success in Minneapolis during the 1946 epidemic when an unusually high percentage of the cases was bulbar in type and many of these patients had breathing difficulties.

Spasm of the muscles of breathing is almost always a factor in poliomyelitis patients with breathing difficulties, and many patients can be relieved greatly by hot wool compresses laid lightly on the chest and abdomen, and changed about as rapidly as freshly heated pieces can be supplied. Most hospitals have special equipment for heating and wringing these compresses, but in homes they can be prepared satisfactorily by cutting old woolen blankets into suitable pieces, which are then boiled and, when boiling hot, are passed twice through an ordinary laundry wringer. This leaves them still hot but dry enough so that they won't burn. When no wringer is available, satisfactorily hot compresses can be prepared by rapidly ironing with a very hot iron, at the patient's bedside, the pieces of blanket which have been wrung out of water as hot as can be tolerated by the hand.

Many patients who seem to be progressing toward the stage where artificial respiration is necessary can be kept breathing adequately by the use of oxygen and hot compresses. Where there are bulbar manifestations, it is particularly important that this be done if possible. But in patients with the spinal form with failure of innervation of the intercostals and diaphragm, artificial respiration becomes necessary at times.

Doctors of wide experience vary greatly in their opinions concerning when artificial respiration should be given. Some would use it at the earliest evidence of breathing difficulty; others postpone its use until the last moment before coma appears. There are advantages and disadvantages to both usages, so that in any given case the decision as to when to start artificial respiration must depend on a number of factors.

The progressive clinical stages of anoxia must be understood. At first there is restlessness, a beginning of anxiety, and possibly some difficulty in sleeping. Then the respiratory rate, excursion, and effort become increased. The patient becomes disinclined to talk, and when asked to count says fewer and fewer numbers in each breath. Cyanosis appears. He stops answering questions and a curious twitching develops around the corners of his mouth, just as coma reveals a dangerous degree of anoxemia and approaching death.

The natural thought is, why not give artificial respiration early and forestall these later stages? There are definite drawbacks and disadvantages to so doing. The respirator, a machine of several different types, in which the patient is placed entirely except for his head, which protrudes out through an end, accomplishes artificial respiration by means of an electrically driven pump which automatically and rhythmically raises and lowers the pressure in the respirator around the patient's chest. In the last fifteen years or so, respirators have been brought to a high degree of mechanical perfection but their use has its definite drawbacks. Patients rapidly become psychologically dependent on artificial respiration. While in the respirator, they develop improper patterns of breathing and also while they are there it is almost impossible to give them the hot applications and passive motion they should be having. Furthermore, patients with breathing difficulties who have been made to carry on without artificial respiration seem to have better chests afterward and a lesser tendency to a complicating atelectasis than those who have been put in respirators. Bulbar patients with much mucus in the pharynx practically invariably do badly in a respirator unless tracheotomy is first done and suction is used to keep the trachea clear of mucus.

However, there are three clear indications for the use of artificial respiration. The first one is to relieve the patient who is on the verge of coma due to anoxia, who, despite nasal oxygen, is developing twitching around the corners of his mouth. He needs immediate help. The second is to benefit the acutely ill patient who, because of a moderate but definite difficulty in breathing, has been without sleep for several nights and is getting tired. He must have the sleep which only artificial respiration will permit. The third, is to help the patient who has been in a respirator and is out by day but cannot sleep at night due to the continual muscular effort required for breathing. He must have artificial respiration each night or every other night so that he, too, may have the rest that only sleep can bring.

At this point it must be noted that sedation of any sort is strongly contraindicated both for the patient who at any stage of the disease is having breathing difficulty and for the patient with an acute condition who may develop it. Artificial sleep may suppress a patient's essential efforts to breathe, and patients have ceased breathing in their sleep when the sleep was forced on them by sedation.

To be able to use a respirator properly, both doctors and nurses should have special training, including being themselves put in a respirator for a short period —a very educational experience. In general, special efforts should be taken to see that the patient is made as comfortable as possible both in mind and body.

If there is time, he should be tactfully and reassuringly prepared for the experience, and he should be told someone will be constantly at his service. As he is placed in the machine, soft cloths must be used to keep the rubber collar from rubbing on his neck. A large pillow placed under his knees makes his back much more comfortable. In running the machine, negative pressure should be used and the amount of pressure and the rate of the machine should each be adjusted to the patient's comfort. Most adults do well at fourteen to sixteen breaths a minute and a negative pressure of 12 to 14 cm. of water. Occasionally the use of a respirator for only thirty to sixty minutes at a time is sufficient to rest the patient and to enable him to breathe again for a time with the help of oxygen only. However, most patients, once they are in a respirator, like so well the relief from the effort of breathing that artificial respiration has afforded, that it becomes very difficult to wean them from the machine in less than two or more weeks.

When artificial respiration is imperative to maintain life and a respirator is not immediately available, breathing can be maintained by manual artificial respiration, or with less effort by means of a seesaw. If the patient is tied on a window shutter or ironing board which is then balanced over a horizonal banister or the high foot of a bed, respiration can be maintained by the slow, rhythmical, gentle tilting of the seesaw, each elevation of the patient's feet causing the abdominal viscera to push the diaphragm up and each lowering to pull the diaphragm down.

Such are the measures which one may use in an attempt to tide the seriously ill patients over the acute stage of the infection. Fortunately, in most epidemics, patients with bulbar or respiratory difficulties comprise a small minority of all cases. Most of the patients with recognizable weakness are pure spinal cases, that is, have no evidence of bulbar involvement, and there are many more additional patients whose condition can be recognized as "acute poliomyelitis without paralysis," if this diagnosis is kept in mind as a possibility whenever there is poliomyelitis about. When a patient develops fever, vomiting, some tightness and tenderness of the neck, back, and hamstrings, irregular reflexes tending to disappear, and twitchings and tremors of various muscles, a lumbar puncture should be done, unless definite paralysis also is present, making the diagnosis fairly obvious. If an increase of cells in the spinal fluid is found, numbering possibly twenty to 200 or 300 or more, this added circumstantial evidence strongly suggests the diagnosis of poliomyelitis. This being a virus disease, the blood count is usually that of any virus infection; there is little if any increase in the total number of leucocytes or of the percentage of polymorphonuclear neutrophiles. An appreciable leucocytosis should give warning of a possible complicating bacterial infection. There is no pathognomonic symptom, sign, or useful clinical test to confirm the diagnosis.

Thus, when a doctor has satisfied himself that there is no immediate danger to life, that the patient has neither bulbar nor respiratory difficulties and yet apparently has definite poliomyelitis with or without paralysis, he then outlines and institutes the details of treatment somewhat as follows:

The patient is put to bed on a firm mattress with a bed board immediately beneath it to prevent sagging of the mattress and particularly of the patient's back. He is dressed in a minimum of clothing, perhaps a loin cloth, and a pajama shirt put on backward and thus easily removable. A vertical board at the foot of the bed keeps the weight of the bedclothes off the patient's tender legs and can later be used for postural training. Older children and adults are encouraged to lie on their backs with their feet against the footboard and with a slight blanket roll under their knees to take some of the strain off the lumbar region and prevent hyperextension of the knees. No pillow is allowed under the head because it would increase the tension of the posterior neck muscles. Little children are allowed to choose any position in which they are most comfortable, usually a side position with hips and knees flexed. When comfortable, any person, sick or well, is more relaxed than when uncomfortable.

Proper isolation measures are at once instituted, varying according to the regulations of the local health authorities. Since the virus has been found in the secretions of the nose and throat for the first four or five days of the fever, respiratory precautions should be observed for the duration of the fever and a day or two more. This means that gowns are worn and all the details of a proper isolation technique are carefully observed. Masks are thought by many to give a false sense of protection and to be more harmful than helpful. They are not used on many poliomyelitis services.

Because the virus is found in the stools of patients an average of two or three weeks but occasionally longer, regulations usually call for sterilization of the stools during the isolation period. Inasmuch as most of the patient's contacts are also probably passing the virus in their stools without any supervision or control, it would seem futile to sterilize one person's stools and ignore those of many others. However, people caring for patients with acute poliomyelitis should remember that the stools contain virus, and wear rubber gloves while handling contaminated bed pans. Furthermore, open privies should be heavily chlorinated, and also well screened against flies, which have been proved to be able to carry the virus and to infect clean food.

The patient being properly put to bed and isolated, he should be provided as much rest and comfort as possible without the use of sedation. Sleep should never be disturbed for routine measures. Examinations should be at a minimum, and handling should always be gentle. Pain is in part responsible for the patient's increased muscle tensions, and should be combatted. For this, moist heat, in the form of hot packs is very helpful. These packs are usually of three layers. The layer applied to the patient is a double thickness of wool, such as a blanket, cut to fit the muscle groups that are tight. The next layer is some waterproof material such as koroseal or a piece of a shower bath curtain, and the outer layer is another piece of wool to hold in the heat. The packs are perhaps most effective when wrapped around the affected parts of the extremities and of the body, but laid-on packs applied to the neck, back, and lower extremities of the patient in the prone or face-down position, and repeated every fifteen minutes for an hour, and for three or four such hours a day, are also beneficial

and involve very little actual handling of the patient. In either case, the inner layer of the pack should be boiling hot and then passed twice through a tight wringer, or the wool may be steam heated.

The use of hot baths as advocated by Gurewitsch is also very beneficial and often more easily accomplished. The patient is gently placed up to his neck in water at body temperature and then hot water is added to raise the temperature of the bath to 104° F. The patient is kept in this for fifteen minutes but cold cloths or an ice bag must be applied to his head, and as for all patients whose treatments cause much perspiration, fluid and salt losses must be replaced by the administration of large quantities of fruit juices and water and a salt tablet. Because of the danger of fainting, a patient in such a bath should never be left alone, even for only a moment.

In homes where neither packs nor tubs can well be arranged, an ordinary cotton sheet wrung out of cool tap water at 60 to 65° F. can be wrapped about a naked patient, folds of the wet sheet being tucked between the legs, and between the arms and the body. A blanket is then wrapped around the patient from his head to beyond the toes and, except in hot weather, a second blanket is laid on top. In ten minutes the patient is warm and beginning to perspire, and presently the patient may relax and fall asleep. Such packs can be applied twice a day and can be left on two or three hours each time. They are especially helpful for restless little children and for patients with a wool idiosynerasy.

Particularly in the acute stage of this disease, the patient's ability to empty the bowel and bladder should be noted carefully. Adolescent boys are particularly likely to be unable to void and frequently have to be helped with catheterization. Where the difficulty persists more than a day or two, it is usually wisest to install a self-retaining catheter and to administer small doses of sulfadiazine by mouth for urinary antisepsis. For apparent constipation, cathartics often cause increased intestinal peristalsis and cramps without accomplishing an emptying of the rectum, and it is wiser during the acute stages of poliomyelitis to depend solely on sodium bicarbonate enemas given every other day. In the subacute and chronic stages, milk of magnesia may be tried.

The use of the stimulants oxygen, caffein, and neosynephrine has already been mentioned. Of other medications, aspirin may be used freely if desired and makes a fair proportion of patients more comfortable. It is best given with an equal amount of sodium bicarbonate, and when there is some food in the stomach. Any acutely ill patient, even one without apparent evidence of breathing difficulty, may, in the course of two or three hours, develop enough weakness or tightness of the muscles of breathing to necessitate conscious effort on the part of the patient to keep going, hence sleep-producing medication for such a person is strongly contraindicated because he may stop breathing in such sleep. This prohibition cannot be repeated too often.

Of drugs intended to relax spasm, two might be mentioned, not for recommendation as yet, but because of an already wide interest in each. The first, curare, acts in effect to raise the barrier to nerve stimuli at the motor end-plates, and hence shuts off some of the motor impulses that are increasing muscle ten-

sion. A curare product known as intocostrin is rapid in its action, and, depending on the route of administration, takes but a few minutes to cause relaxation. Because its effect also wears off quickly, the possible relaxation obtained from its use is very temporary and the margin of safety is narrow. Another preparation known as tubocurarine is administered in peanut oil, with the result that such relaxation as it produces lasts more than twenty-four hours. The use of any curare preparation in poliomyelitis is not sufficiently standardized to be recommended as yet, and there have been unfortunate accidents resulting from its injudicious use. The drug should have much more study under properly controlled conditions before being advocated for general use.

Neostigmine, the pharmacologic antidote for curare, lowers the barrier at the motor end-plates and hence facilitates the passage of stimuli from the central nervous system to muscles. Its use for the relief of spasm is not yet substantiated. On the contrary, when used in Parkinson's disease, it markedly increases muscle tension. Theoretically, in poliomyelitis it might make it easier for the few remaining healthy neurons innervating a particular muscle to function, and in actual use after spasm has gone, it occasionally seems to increase endurance as shown by repeated motions, but there is no increase of strength. The drug's field of usefulness in the treatment of acute poliomyelitis is not yet established.

Thus far in this account of the treatment of acute poliomyelitis the measures recommended have been those which will be carried out by the pediatrician, and the nurse or mother. But in the subacute stage, and even in the presence of the fever of the acute stage, other specialists should play a part in the care of the patient and it is well for the pediatrician to know when to call on them and what to expect of them.

As soon as the diagnosis of poliomyelitis is made, and it is found that there are no bulbar or breathing difficulties, it is well to have the physiotherapist visit the patient to make his acquaintance and start to attract his confidence and friendship. An attempt may be made to determine and record the extent of muscle spasm on a so-called flexibility chart, but in order neither to fatigue nor hurt the patient, the physiotherapist does this very gently and in several installments. When the fever is essentially gone, the physiotherapist may begin gentle passive motion of the extremities in what is known as tendon stimulation, but she always does less than will cause the patient fatigue and discomfort. Then, as the days or weeks pass and tenderness and spasm disappear, this specially trained worker is given a larger and large proportion of the care of the patient as she leads the patient through the steps of passive motion, active motion without weight bearing, exercising for control, then functional exercising, and finally exercising for strength, and for social rehabilitation.

The efforts of the physical therapist can early be supplemented by occupational therapy. A psychiatrist also is often most useful in helping both the patient and his family to prepare for a life which may have great restriction—for moving, figuratively speaking, "from an old familiar room to a new room which must be furnished as best one can." Thus did a famous preacher put it to a young lady obviously destined to be terribly restricted by her poliomyelitis.

The orthopedist has an important place, although not in the care of the acute disease. Removable plaster splints or shells have their usefulness as early as the subacute stage to prevent a restless child's keeping an extremity in a position which aggravates muscle shortening, such as sitting on his feet in plantar flexion when the calf muscles are tight. When the first weight bearing is desired, mechanical support for a very weak back, abdomen, or extremity may be necessary. And finally, at least two years after the onset of the infection, the expert and specialized services of the orthopedist are often needed for a reconstruction operation that will help in the final step of the patient's care, that of social rehabilitation.

The pediatrician's responsibility to the poliomyelitis victim's family does not end with his care of that patient. If there is a clearly recognizable case of the disease in a large family it is usual to find that several of the other children have some kind of minor illness more or less at the same time as the onset of the patient's poliomyelitis. These minor illnesses, a head cold, a slight indigestion, or a slight headache and fever, might very well be trivial poliomyelitis infection, and should be treated as such by instituting prompt and complete bed rest. By such a procedure it is possible that the infection can be kept from being aggravated into severe paralysis.

This point naturally leads to a discussion of possible prophylactic measures. When poliomyelitis is present in a community, doctors have the great responsibility of informing the lay population how, according to our present knowledge of the etiology and nature of the disease, the ravages of this terrifying infection can best be minimized. It is now believed that the virus, like that of many other infections such as measles and influenza, is easily passed from person to person and enters the contact through the nose and throat. It apparently moves on down the alimentary canal to be passed out in the stool. Under favorable conditions it invades the mucosa and travels by regional nerves to the central nervous system. In a comparatively small number of those infected, the infection is sufficient to cause an illness, and in a still smaller prooprtion to cause paralysis. In an epidemic, probably nearly everyone is infected, despite any regulations of quarantine against the spread of the illness. Hence, efforts should be directed toward minimizing the effects of the disease in those infected. Unfortunately, there is only a little known as to why one infected person escapes and another is hard hit. At the present time, the following suggestions seem reasonable.

1. Avoid exhaustion due to chilling or fatigue. Animal experimentation and clinical observation strongly suggest that persons incubating the disease who become chilled or overtired are more apt to have the severe forms of the infection.

2. Similarly, persons whose poliomyelitis has begun apparently can aggravate its ravages by not getting immediate rest. Hence, in the presence of poliomyelitis, every person with even what seems a minor illness should go to bed and obtain complete rest until quite well again.

3. The mucous membranes of the nose and throat should be kept in as healthy a condition as possible. The incidence of severe bulbar cases is some

sixteen times more frequent in children who have had recent tonsillectomies than in others. Hence, the removal of tonsils and adenoids should be postponed until the epidemic is well past. It is possible that a tooth extraction may open a portal of entry, and there are those who suspect even the common cold as facilitating the passage of the virus through the mucous membrane.

4. There is no advantage in using drugs, chemicals, sulfonamides, antibiotics, or such mechanical measures as nose drops or gargles in an attempt to ward off the infection. There is no evidence that any such supposed preventive is of value.

5. The use of any water that is possibly contaminated with sewage for drinking, swimming, or washing utensils, should be avoided. The virus has been found in sewage-contaminated streams, but water borne epidemics have not yet been proved.

6. Similarly, flies should be destroyed and food should be kept protected from flies. It has been proved that flies collected in an epidemic area can harbor the virus and can infect clean food sufficiently to pass the infection on to monkeys fed this food.

7. Unnecessary personal contacts should be avoided. Close contact undoubtedly increases the dosage of an infection, so congested places should be avoided, and such acts as the sharing of a lollipop or whistle, or of a drinking glass should be omitted. There is probably little to be gained by running away from an epidemic; one is probably already infected. On the other hand, one might well hesitate before moving from a clean community to an epidemic area.

SUMMARY

An attempt has been made to describe measures which should be instituted when a doctor undertakes to care for a patient with acute poliomyelitis, and why these measures are indicated. The care of those patients where life is most in danger, that is, of patients with bulbar and respiratory difficulties, is first described, followed by that of patients with the more common and less urgent spinal form. How the efforts of various specialists are tied together, is followed by mention of the importance of looking for otherwise unrecognized cases in the patient's family. Finally, some suggestions are given for prophylactic measures to be observed in the presence of an epidemic.

Clinical Conference

CONFERENCE AT THE ST. LOUIS CHILDREN'S HOSPITAL, MAY 23, 1947

DR. ALEXIS F. HARTMANN, CHIEF OF STAFF

Case 1. Adenoma of the Adrenal Cortex

DR. RICHARD HAWKINS.—The first patient is D. Z., 18 months of age. She was born at term following a normal pregnancy. Delivery was normal and the neonatal period was uneventful. She was breast fed for two months, then fed an evaporated milk formula, and had developed normally throughout infancy until about eight months ago. At that time (October, 1946) she was seen by a private physician. She seemed to be quite normal, although somewhat large for her age. Her brother is also large for his age. During the previous eight months the patient seemed to be growing rapidly. The patient was seen again last week, and the examining physician noticed a profuse growth of pubic hair and a very great increase in height and weight. The parents stated that about three months prior to the last visit the patient had begun to develop a growth of pubic hair which had increased progressively. The parents had noticed the rapid increase in height and weight. When questioned about the pitch of the baby's voice, they stated that it had become somewhat husky during the last three months. The patient was hospitalized for observation and treatment. On admission here, physical examination revealed a child who was large for her age and plump; the skin was darkly pigmented throughout, but the father is also of dark complexion. The eyebrows were dark, there was hair on the upper lip and a little growth of hair about the nipples with no breast tissue present. The examination of the abdomen revealed no masses and no palpable viscera. About the genitalia there was a striking growth of pubic hair with distribution of the male type, and in addition there was a growth of vulvar hair. The labia majora were large; the clitoris was greatly enlarged for this age. The remainder of the examination was not revealing.

The urine was normal; hemoglobin was 16.9 Gm.; white blood cells were 11,950; the red blood cells appeared normal on stained specimen. A glucose tolerance test (Chart 1) gave the following results: 60 per cent at fasting; at ½ hr., 106 mg. per cent; at 1 hr., 100 mg. per cent; at 2 hr., 92 mg. per cent; at 3 hr., 83 mg. per cent. During the past seventy-two hours she has been on total urine collection. Dr. Allen's laboratory will do 17-keto-steroids and also test quantitatively for pregnandiol. X-rays of the skull, abdomen, and long bones have been taken.

DR. PAUL ZENTAY.—The enlarged clitoris resembles a hypospadias.

DR. JAMES LITTLE.—The flat plate of the abdomen showed nothing particularly abnormal, and the bone development as shown in the wrist joint was within normal limits for the child's age. The only thing of interest which

we found was in the skull film. In the central portion of the skull on the right side, there is, apparently, a small area of calcification. We asked for a right stereoscopic view to see if we could localize it more definitely. We feel that it will not be significant when we get it, but that it should be traced down to be sure of the possibility that there may be calcification within the brain. As well as one can tell, the chest film with its double exposure taken in expiration rather than inspiration does not appear abnormal. The outer lung fields are clear; the cardiac shadow is not unusual.

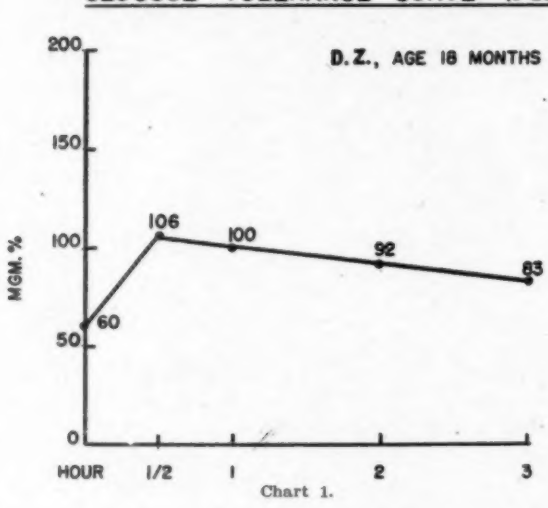


Chart 1.

DR. ALEXIS HARTMANN.—You do not think the calcified area in the skull film is artifact?

DR. LITTLE.—It well may be.

DR. HARTMANN.—Do you think the sella turcica is within normal limits?

DR. LITTLE.—Yes.

DR. ZENTAY.—Is there any abdominal mass visible?

DR. LITTLE.—No, we could not see any. The gas pattern was well distributed, and didn't seem to be displaced by any solid mass. The kidney shadows could not be made out. The psoas shadows are of good outline.

DR. ZENTAY.—We hoped that Dr. Allen would discuss this case, but he is unable to be here. As you remember from the history of this child, there was a tremendous somatic growth; actually, the child gained 13 lb. in about six or seven months, and the external genitalia, including the clitoris, definitely showed the tendency to male development. There is marked hirsutism not only

in the pubic area but beginning on other parts of the body. As far as can be ascertained from our findings, the internal genitalia (we have done no pelvic nor rectal examination) appear to be within normal limits. That, of course, should be confirmed by more intensive examination. From the fact that this child has shown rapid growth, masculinizing changes, and precocious sexual development, we may assume even before we get all the laboratory data that we are dealing with an adrenal tumor. What the nature of the tumor is, we do not know. It may be benign or malignant. That can be determined only after operation is performed, and the tumor is examined and possibly removed. It is known from the few cases in the literature (there are not too many, and the whole picture of sexual precocity is still confused) that adrenal tumors do produce this syndrome, and they may occur at almost any age. A series of three cases was reported from the Henry Ford Hospital.[1] In one the process began at 4 months of age. The tumor was a malignant one arising on the face with metastasis into the adrenal gland, and it produced the type of picture seen here. The child died at 25 months of age. Other similar reports are in the literature. The older the child is, the more difficult it becomes to differentiate between the different types of tumors responsible for these changes. If Dr. Allen obtains laboratory findings which are in harmony with the physical findings, the next step will be to do a laparotomy to explore at the same time the ovaries and the adrenal glands. It seems safer to rule out ovarian tumor and then proceed at the same operation to remove the adrenal gland.

I should like to mention the different types of sexual precocity which have been described. There is an interesting article by Novak[2] who discusses the various forms of sexual precocity and also emphasizes that there are cases of so-called constitutional sexual precocity, a type which has not received enough attention in the past. Most of the cases reported in the literature are either of this type or are cases of adrenal tumors or ovarian tumors. There are several other types of sexual precocity described. There is the so-called pineal tumor. You remember we have seen a few here in recent years, and there has always been a tremendous development of the external genital organs, and a marked growth of the body in general. From our point of view, this possibility can be ignored more or less, inasmuch as pineal tumors and sexual precocity as the result of such tumors have been recorded only in boys. There is only one case reported in the entire literature in a girl, and that is questionable. The problem of mechanism of action of the pineal body tumors still remains: that is, whether the effect is produced by internal secretion of the pineal or by pressure of the tumor on the midbrain and regulating centers in the midbrain. There are two types of ovarian tumor, granulosa cell and theca cell, known to cause sexual precocity. The difference between the adrenal tumors and ovarian tumors lies in the tendency of ovarian tumors to produce a more feminine type of sexual precocity. There is usually well-defined vaginal mucosa, sometimes discharge, and menstruation may begin very early. Usually the ovarian tumor can be palpated and can be demonstrated on operation. After removal there usually is a great deal of improvement. Then there is the so-called cerebral type of sexual precocity. Tumors in the cerebrum, particularly in the fourth

ventricle or in the midbrain, or tumors in other parts of the brain interfering with the midbrain may cause sexual precocity. There have been cases described where encephalitis, particularly the type of encephalitis that we used to see twenty years ago (the type A or von Economo type), seemed to lead to precocious sexual development. Tumors of the hypophysis may cause sexual precocity, but again there is a question as to whether the internal secretion of the anterior lobe or disturbance of innervation coming from the midbrain is responsible for the sexual development.

The other form particularly emphasized by Novak is the so-called constitutional type of sexual precocity. Here the important thing is that the child is perfectly normal in every other respect. There is no change in body structure, but at any age, as early as a few months or a few years, the development of secondary sexual characteristics (increase in the size of the breasts and development of pubic and axillary hair) begins. These are the children who may become pregnant. You remember the Peruvian child who, at 5 years of age, delivered a perfectly normal baby. There are other reports in the literature of very early pregnancies. These girls menstruate very early, and in contrast to cases of sexual precocity due to ovarian tumors or other causes they not only menstruate but also ovulate, and, therefore, there is always danger of insemination. These children, in spite of their sexual precocity, grow and develop normally, and are normal by the time they reach the usual age of puberty, and no further difficulty arises. The cases which Novak calls constitutional sexual precocity present no serious problem from the point of view of physical development of the child, but they pose important social and psychologic problems, because these girls naturally become very conscious of their difference from other girls and on that basis may develop all kinds of psychic difficulties. They have to be protected from that danger and also they have to be protected from the possible danger of insemination.

DR. HARTMANN.—There are two points that I would like to make, one of not very great importance, the other perhaps of more importance. The older members of the staff must remember a child seen about five years ago, E. B. Both Dr. Allen and I were struck with the resemblance between E. and this girl, and in his characteristic and thorough way Dr. Allen studied the facies of this patient, and said, "I believe the reason this child looks so peculiar is because of the well-marked eyebrows," and we promptly went around and looked at all the other children on the ward. There was no child at or near this age with anything like the eyebrow development which this child has, and I think that is what is characteristic of the expression of this girl. E. had similarly well-developed dark eyebrows. The other point that I think is of some importance is this: chances are that this will be an adrenal tumor. Dr. Allen thinks so, and I think you do, Dr. Zentay, and so do I. In any case, a laparotomy will be performed, and if the tumor is found, we expect it to be a unilateral one, and it will be removed. At the moment this child is suffering from hyperadrenalism, and when the adrenal tumor is removed there will still be a normal adrenal left, but the child will then suffer from hypoadrenalism.

E. died postoperatively from signs and symptoms of hypoadrenalism, despite the fact that we were giving what we thought was adequate substitution therapy. I think when this child is sent to operation we ought to be sure to be well-prepared to give all types of supportive treatment for a while, to have special nurses in constant attendance, and have adrenal cortical hormones available, as well as adrenalin, salt, and glucose, to try to prevent the child from going into shock. In the literature, other deaths similar to E.'s have been reported following removal of a single adrenal gland with its tumor.

Addendum to Case 1

After presentation of this case at conference, an intravenous pyelogram was obtained which revealed apparently normal kidneys, but the left kidney was noted to be lower in position than usual. It was apparently displaced downward by pressure from above. The serum sodium preoperatively was found to be 142 millimols, potassium 14.8 mg. per cent, nonprotein nitrogen 26 mg. per cent, and the serum sodium chloride 562 mg. per cent. Serum glucose levels on several occasions were found to be normal. The twenty-four-hour excretion of sodium pregnandial glucuronidate was 14 mg., the 17 keto-steroid excretion was 45 mg. per twenty-four hours.

Laparotomy was performed through a long left rectus incision. Biopsies of skin and subcutaneous tissue in the muscle were taken, and a tumor of the left adrenal gland was removed. The right adrenal could not definitely be palpated. Neither ovary could be felt. Before, during, and after the operation the patient was maintained on large doses of desoxycorticosterone and continuous drip of 10 per cent glucose solution in saline. In addition, whole adrenal gland extract and later lipoadrenal extract were administered. The blood pressure remained considerably elevated (up to 165/105) for several days following the surgery. The postoperative course was relatively smooth. At no time did evidence of adrenal insufficiency (dehydration, hypotension, hypoglycemia) present themselves. The blood pressure gradually stabilized at a level of about 110/60. The serum true glucose was on all occasions within normal range. One week postoperatively the serum potassium was found to be 4.91 meq. (19.2 mg. per cent) and sodium was 138 meq. The nonprotein nitrogen had risen slightly to 34.5 mg. per cent. On the sixteenth hospital day lipoadrenal extract was discontinued, and no further substitution therapy has been given since. There is no evidence at the present time of adrenal insufficiency. The child is happy, playing well, and seems to be in perfectly good health. There has been no marked regression in the secondary sexual development so far.

The pathologist reported that the tumor which was removed was an ovoid mass measuring 6 × 4 × 3 cm. in diameter. It had a capsule, through which could be seen shining, yellowish-pink, tumor tissue. The capsule showed evidence of lobulations beneath the surface. On cut section the tumor bulged markedly above the edge of the capsule and showed a lobulated appearance, with both large lobules and smaller individual lobules within the larger ones. It had a variegated appearance as to color, some areas being bright yellow, others being duller yellow to gray. It was of firm consistency after being fixed.

Microscopically the tumor was seen to be made up of cells which had a polygonal shape, eosinophilic cytoplasm, and a very distinct cellular wall. The nuclear elements were round to oval, and for the most part slightly hyperchromatic; some of the cells, however, showed a syncytial arrangement with three to four large vesicular nuclei lying within the eosinophilic cytoplasm. The cells tended to grow in cords and strands, between which small vascular capillaries could be seen. In some areas the cytoplasm of the cells tended to be clear or slightly granular. No mitotic figures were found. There was a very well-defined capsule, and no tendency for the cells of the tumor to invade the capsule. The skin showed only some increase in the number of hair follicles. There was also some increase in the keratin material on the surface of the skin. The skeletal muscle appeared to be perfectly normal. On the basis of these findings the clinical diagnosis of adenoma of the adrenal cortex was confirmed.

Case 2. Histoplasmosis

DR. JOHN MARTZ.—This child, 3 years old, weighed 8,400 Gm. She had apparently been a normal healthy child until April, 1946, when she developed whooping cough which was complicated by pneumonia. At that time she weighed 32 lb. She was acutely ill for about a month. Following the attack of whooping cough, she continued to have recurrent bouts of fever (during the summer of 1946) associated with listlessness and profuse sweating, but she gained a little weight. Approximately six weeks before admission she began to lose weight and appeared very listless. She was hospitalized at that time in her local hospital and treated with penicillin and blood transfusions because of marked anemia. During this period she developed rather severe diarrhea; she passed numerous, greenish, watery, foul-smelling stools in which, at times, small flecks of blood were seen. X-rays taken during this episode revealed osteolytic processes of the clavicle, skull, and both femurs. At the time of admission to Children's Hospital the patient was markedly malnourished, dehydrated, and athreptic, but was mentally alert. There was bleeding of the lips, gums, and finger nails. There was general lymphadenopathy, most prominent in the cervical glands, which were firm and shotty but discrete. There was a large area of ecchymosis over the left thorax posteriorly. Many white patches were seen on the tongue and buccal mucous membranes. These could not be rubbed off easily. Fluoroscopy of the chest revealed haziness of both lung fields but no notable change in the mediastinum. The temperature was normal. The urine showed a trace of albumin with occasional white blood cells and granular casts. The hemoglobin was 14.4 gm. red blood cells 6,000,000, white blood cells 4,400 with an adequate number of platelets and a marked shift to the left in the differential, showing 2 juveniles, 70 stab cells, 25 segmented cells, and 2 lymphocytes. There were two nucleated red blood cells per 100 white blood cells, and the red blood cells appeared microcytic. The Kline test was negative. The first stool passed after admission was large, quite watery, and very foul-smelling, and contained a moderate amount of blood. The child was given a regular diet, but the diarrhea immediately became quite severe, and the diet was changed to

one high in protein, high in carbohydrate, and low in fat. The baby was given supportive treatment with plasma and glucose intravenously and Ringer's subcutaneously to maintain hydration. The temperature remained for the most part between 38 and 39° C., but on the second hospital day spiked to about 40° C. This was quickly controlled by temperature sponges. X-rays of the long bones and skull revealed healing or healed nutritional disturbances of the bones. There was effusion into both knee joints and a small area of radiolucency projecting into both parietal and frontal bones, the right scapula and both femurs. The lesions in both femurs, the scapula, and skull, suggested either a chronic pyogenic or luetic osteomyelitis or a tumor of the lymphohematopoietic system, such as a chloroma or leucemic infiltration.

One of the cervical nodes was biopsied, and the microscopic section revealed infestation with histoplasma capsulatum. Previous to this, a bone marrow sample had been secured, and some yeastlike particles were seen, both intracellularly and extracellularly. These were considered to be suggestive of histoplasma organisms. A histoplasmin skin test was done on the fifth hospital day, but the child expired on the sixth hospital day before the skin test could be read. Studies done at the time of admission showed prothrombin time, clotting time, and bleeding time within normal limits. Serum nonprotein nitrogen, protein, calcium, phosphorus, carbon dioxide, and chloride were also normal. Blood sugar was 25 mg. per cent. Culture of the gastric juice revealed abundant growth of colon bacillus. There was normal tryptic activity of the duodenal juice, and the cephalin cholesterol flocculation test was reported as 3 plus. Several blood, urine, and stool cultures did not reveal any significant organisms, and routine agglutinations were negative. Clinical diagnoses were: histoplasmosis, generalized; malnutrition, severe.

DR. OSCAR RAMBO (Pathologist).—At autopsy we found the emaciation and dehydration as noted in the physical examination, and in addition there was an ulcerated area which had slightly raised edges covered by a greenish exudate in the skin over the left posterior lumbar region. On examination of the internal structures, significant findings were in the gastrointestinal tract. In dissecting the neck organs we found ulcerations at the lateral margins of the tongue. These ulcers were pink in color, and the edges were granular and slightly elevated. In the cervical region were numerous enlarged, yellowish nodes which were clustered about the submaxillary glands. There were fewer of these nodes about the upper part of the trachea. In the mediastinum we found no similar lesions. In the abdominal cavity we found great numbers of huge nodes in the mesentery of the entire intestine. The peritoneal cavity contained 25 c.c. of dark yellow fluid. In the solid viscera the only granulomatous lesions noticed were nodules of yellowish color with areas of caseation in both adrenal glands. In the intestine the changes were most notable in the jejunum. The first change consisted of very fine yellowish-brown areas in the villi which appeared grossly to be distended firm lacteals. In the ileum we found a few similar areas. Most notable were numerous ulcerated lesions which were round or ovoid, the ovoid ones having their greatest diameter perpendicular to the long

axis of the intestine. These lesions were ulcerated centrally and were firm and yellow at the periphery. Some of the ulcers were hemorrhagic. Similar lesions were found in the colon, in the appendix, and in the rectum. We also found masses of large yellowish nodes about the pancreas. A few of these showed small foci of caseation. We examined the medial portion of the right clavicle, and the central portion of the bone seemed somewhat soft. Examination of the calvarium showed several translucent areas in the frontal and parietal bones, circular in shape and approximately 1 cm. to 1½ cm. in diameter. There was no appreciable difference in the consistency of the bone in these areas.

Histoplasma capsulatum was cultured from the lymph nodes by Dr. Beamer.

DR. MARGARET SMITH.—The distribution of the pathologic changes appears to be of significance in relation to the route of entry of the organism. I think the fact that there is a marked involvement of the intestinal tract and the mesenteric lymph nodes and the cervical lymph nodes, but no involvement of the mediastinal nodes or of the lungs, is of interest. The other cases that we have observed in children fall into two groups: one in which the lungs were extensively involved with little change in the intestinal tract, the other with marked involvement of the intestinal tract with much less conspicuous change in the lungs. In this case, as far as the gross changes are concerned, there is nothing in the lungs or in the mediastinal or tracheobronchial lymph nodes. It seems almost inescapable that the route of entry here must have been through the intestinal tract rather than through the lungs. Another thing that we thought to be of interest was the very marked involvement of lymph nodes in the mesentery and the quite remarkable pattern in the intestinal mucosa apparently due to filling of the lacteals and lymphatic spaces with organisms.

Slide 1.—This is a section of one of the abdominal lymph nodes. The section shows destruction of the normal architecture of most of the gland. The sinuses are filled with large cells. There are foci of necrosis, and throughout the nodes, not only in the lymph sinuses but in the lymph cords, are large mononuclear cells and a small number of multinucleated giant cells. In some parts of the section a few small lymph follicles can be seen, but in general the architecture of the node is entirely replaced by the granulomatous reaction.

Slide 2.—This is a large multinucleated giant cell such as was seen in the sinuses of the node. We see the many encapsulated yeastlike organisms in this large cell. One sees the definite capsule of the organism and the central yeastlike body with eccentric arrangement of the chromatin material. (Fig. 1.)

Slide 3.—This is a section of an intestinal ulcer (Fig. 2) with necrosis of the mucosa and extension of the granulomatous reaction in the muscle layer. When the margin of this ulcer is examined with a higher magnification we find many of the large mononuclear cells and multinucleated giant cells containing the characteristic organism.

Slide 4.—This is a section from one of the areas which showed the fine, interlacing, yellowish lines on the surface of the mucosa in the gross. All the villi contain large phagocytic cells, some with several nuclei, and other, smaller ones with only one nucleus (Fig. 3). This type of lesion was most extensive in the jejunum. Each villus was filled with these cells without necrosis or ulceration of the mucosa.

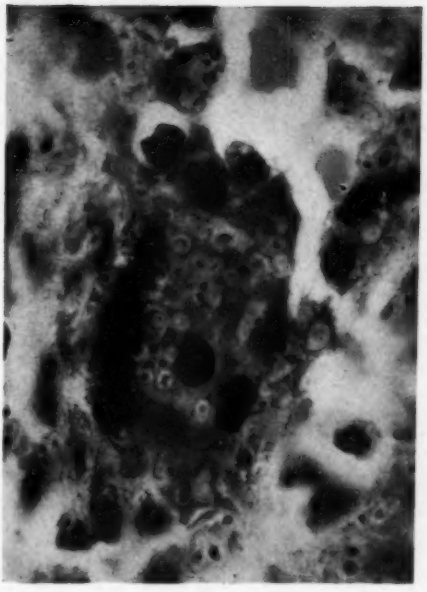


Fig. 1.

Fig. 2.

Fig. 1.—Giant cell containing the organism *Histoplasma capsulatum.*
Fig. 2.—Ulcer of colon.

Fig. 3.

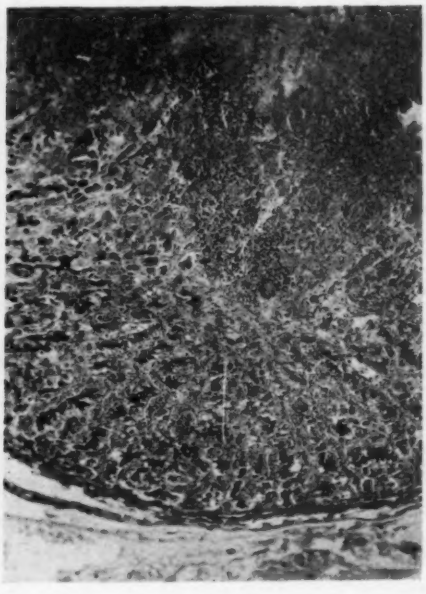


Fig. 4.

Fig. 3.—Intestinal villi showing infiltration of large mononuclear cells and multinuclear giant cells containing organisms.
Fig. 4.—Large area of caseous necrosis in the adrenal gland.

Slide 5.—One of the large multinucleated cells in a villus (Slide 4) is seen and another smaller cell, both containing the characteristic organisms. These sections show particularly well the capsule about the yeastlike organism and the eccentric arrangement of the chromatin material within the yeastlike cell.

Slide 6.—This is a section from the bone marrow of the vertebra. There is marked interference with the formation of blood. There are few normal blood-forming cells. Many foci of necrosis are present. Large mononuclear cells occur about these foci of necrosis.

Slide 7.—This section is from the clavicle and shows again areas of necrosis with deposits of fibrin, edema of the marrow, and infiltration by large phagocytic cells containing the organisms.

Slide 8.—Shows a higher magnification of these large phagocytic cells containing a great number of organisms.

Slide 9.—This is the adrenal. I wanted especially to show this slide (Fig. 4) because the adrenal was the only one of the solid viscera that showed gross lesions. There is a large focus of caseous necrosis. One can recognize the small organisms in large phagocytic cells surrounding the area of necrosis. I think this is of some interest because among the adult cases of histoplasmosis we find that there are a number in which the lesion in the adrenal has been the most conspicuous part of the disease. We had one instance during this last year of an elderly man with an undiagnosed febrile disease and, terminally, some symptoms consistent with Addison's disease. At autopsy the most conspicuous change was in the adrenals, which were replaced by areas of caseation. There were caseous lesions in the lymph nodes and only recent small granulomatous lesions in the liver and spleen.

Slide 10.—The liver in this case showed no gross granulomatous lesions. The liver was a little large, due chiefly to congestion. The sinusoids are distended with red cells and the Kupffer's cells are quite prominent in this section. We found one microscopic granulomatous lesion. This was the only one in the section.

Slide 11.—The lung shows an interstitial bronchopneumonia, but no organisms were found.

DR. PARK J. WHITE.—Dr. Smith, will you discuss the specificity of the histoplasmin test?

DR. SMITH.—I know only what has been reported in the literature. I understand that there is some question concerning the specificity of the antigen now used and that the suggestion has been made that an antigen derived from the mycelial form of the organism may be less specific than an antigen made from the yeastlike form. The thing of interest is, of course, that many positive reactions have been observed in individuals from this part of the country.

DR. JOHN LYNCH.—As far as this test is concerned, we have done 500 here at Children's Hospital since last November, and I am not quite sure what conclusions we can draw. The percentage of positives is around 15 per cent; however, as the age increases (I think we only have three positives under 2 years of age) the percentage of positive reactors becomes as great as 50 in the older age groups (14 to 15 years). There is no correlation, as far as I can see, with the disease the patient has or with the chest film, and we have had no proved cases of histoplasmosis in the patients who reacted positively to the antigen. One interesting thing is that the positives seem to be more frequent

in cases with some type of chronic disease such as bronchiectasis or chronic urinary infection. We did have quite a number of positives on surgical ward, but we don't have chest films on all these patients. We are still in the process of trying to correlate x-rays and clinical findings.

DR. MARTZ.—Dr. Lynch, is there any correlation between the presence of allergy, such as asthma or allergic rhinitis and eczema, and the positive tests?

DR. LYNCH.—As far as I know, there is none. I think we have had two cases of asthma with positive histoplasmin tests. There were no cases of eczema.

DR. SMITH.—Have you made any attempt to find out where these particular children have lived—whether in the country, city, or in Missouri or elsewhere?

DR. LYNCH.—We haven't done that yet.

DR. LOGAN MEWHINNEY.—Dr. Little has some x-ray films on this child.

DR. JAMES LITTLE.—The most striking findings in the x-rays are in the skull films. I think even from a distance you can see these moth-eaten areas throughout the frontal and parietal regions. They show up in all the skull films. The first thing that we thought of was a luetic process. We couldn't find any reference to this type of lesion occurring in histoplasmosis so that it will be interesting to watch from now on to see if we can find this type of lesion in other cases of histoplasmosis. As far as the clavicles were concerned, our film did not show much, but there are areas here in the right scapula which are suspicious.

The long bones showed some changes, and you can also see the marked thickening of the periosteum on the shaft of the femur and some of the destructive radiolucent areas in the bone adjacent to that periosteal reaction. I do not know if there is effusion into the knee joint. The apparent presence of fluid might be illusory due to wasting of the tissues above and below the knee. There is flaring of the epiphyseal portion of the bone, radiolucency, and marked thickening of the periosteum on the inner aspect of both tibias which suggested possible previous deficiency disease which had healed or was in a healing state.

Case 3. Chronic Lymphatic Leucemia

DR. RICHARD HAWKINS.—The next case is that of S. J. T. who is now 3½ years of age. She entered the hospital four days ago. This is her third hospital admission. The first admission was from Feb. 12, 1946, to Feb. 25, 1946. At that time she entered with the chief complaint of pallor. There was a history that at the age of 5 weeks she was noted to have an enlarged spleen and anemia. She was, however, asymptomatic. No treatment of any sort was given at that time. She was seen by a physician the next time at the age of 5 months. At that time she had an enlarged spleen, enlarged cervical

nodes, and anemia. She was hospitalized elsewhere for one month. She presumably had transfusions while there. The hematological findings are presented in Table I. In January, 1947, one month prior to admission, she had a sore throat and a flulike episode. Also, at that time, she lost her appetite, became listless, and seemed to become more pale.

TABLE I. S. J. T.

DATE	AGE	PERIPHERAL BLOOD									
		HGB.	R.B.C.	W.B.C.	EOS	BAS.	STAB.	SEG.	LYM.	MONO.	PLATELETS
6/ 7/44	5 months	13.7	4.64	60,850	–	1	1	19	78	1	–
6/ 9/44	5 months	–	–	–	–	–	–	–	–	–	190,000/c.mm.
6/22/44	5½ months	10.0	4 06	28,200	–	–	–	10	88	2	–
2/12/47	3 years	8.9	2.85	95,000	2	–	1	11	85	1	–
2/17/47	3 years	–	–	–	–	–	–	–	–	–	558,000/c.mm.
2/21/47	3 years	9.3	–	46,500	–	–	–	–	–	–	–
2/24/47	3 years	13.8	–	31,800	–	–	–	–	–	–	–
3/30/47	3 years	10.0	–	10,400	–	–	4	30	60	6	–
5/20/47	3½ years	3.5	1.28	66,700	–	–	2	14	84 (mature)	–	–

BONE MARROW

2/17/47—3 years
WBC—7 segmented cells, 6 stab cells, 4 metamel, 9 myels., 71 small lymphocytes, 1 large lymphocyte.
RBC—7 normoblasts, 1 early erythrobl, 6 late erythrobl.
5/22/47—3½ years
WBC—1 erythroblast/200 WBC, 5 segmented cells, 23 st., 3 metamyel, 7 myel, 60 lym.

On admission here, physical examination revealed a greatly enlarged, firm liver and a spleen reaching to the pelvic brim. Both eardrums were dull and red. There were profuse mucopurulent nasal discharge and postnasal drip. Other physical findings at that time were not of importance. Blood data after transfusion, February, 1947 (she was 3 years old at that time), were as follows: hemoglobin, 8.9 Gm.; red blood cell, 2.85 million; white blood cell, 95,000, with 2 eosinophiles, 1 stab cell, 11 segmented cells, 85 lymphocytes, and 1 monocyte. On her other hospitalization at the age of 5 months, she had had a hemoglobin of 13.7 Gm. (apparently taken after transfusion); the red blood cell count was 4.64 million, white blood cell count, 60,850, 1 basophile, 1 stab cell, 19 segmented cells, 78 lymphocytes, and 1 monocyte. On one of the previous counts, it was recorded that the lymphocytes seemed to be mostly blast forms. The platelet count at the age of 5 months was 190,000 c.mm. Her next admission to this hospital was in March, 1947, at which time she entered for adenoidectomy and transfusion. She was here only a few days. The white blood cell count at that time was down to 10,000 with still a predominance of lymphocytes in the differential, and the hemoglobin was 10 Gm. While she was in the hospital in February, 1947, she had one x-ray treatment to the spleen, and she received x-ray treatments as an out-patient during the time between admissions.

The last admission occurred four days ago. There was a history that six days before the patient had suddenly begun to look more pale than previously, had become listless, lost her appetite, and become quite irritable. This con-

tinued for two days, and four days before admission she developed a fever which ranged between 103° and 104° F. She was seen by a physician who told the parents she was probably developing measles since there was measles in the neighborhood at that time. On the following day, however, the temperature was still elevated, and there were no symptoms or signs of measles. She was seen by another physician who said she had an otitis and prescribed a chocolate medicine and ear drops. On this treatment her fever continued and on the day prior to admission she began to have generalized convulsions which lasted for several hours but abated on treatment by the family physician who again referred her to Children's Hospital. On admission she was extremely pale, but in little distress. It was hard to believe that this anemia had come on as suddenly as the history seemed to indicate. The spleen now was at the level of the umbilicus, whereas previously it had been felt at the level of the pelvic brim. The liver was still enlarged about 1 to 2 fingerbreadths below the right costal margin.

Laboratory examination on this admission revealed normal urine. The red blood cell count was 1.28 million; hemoglobin, 3.5 Gm.; white blood cells, 66,700. The differential was similar to previous differentials in that there were 84 lymphocytes and 16 granulocytes. The lymphocytes were of the small, mature type. Platelet count at this time was 626,000 per c.mm. The hematocrit was ten on this admission. No reticulocytes were seen. The indices revealed anemia of a slightly hypochromic microcytic character. A bone marrow examination was done yesterday. The results are shown in the chart. Previous bone marrow examination done in this hospital on the first admission showed a large number of lymphocytes, mostly of the small type. The normoblasts were 7, early erythroblasts 1, late erythroblasts 6, giving a total of 14 red blood cells per 100 white blood cells. In contrast, on this admission the bone marrow showed 60 lymphocytes, 23 stab cells, 5 polymorphonuclears, 7 myelocytes, and 3 metamyelocytes. Erythroblasts on this admission were 1 per 200 white blood cells. They were very rare. Other laboratory data was reported as follows: the icterus index was 6, and the quantitative urine urobilinogen was .46 Ehrlich units for two hours, which is within normal limits. The patient has received two transfusions on this admission. The first transfusion brought the hemoglobin up to 9 Gm.; she received another full transfusion yesterday.

DR. JEAN HOLOWACH.—This patient is presented this morning as a diagnostic problem. Several points should be clarified before the discussion. It was mentioned that at 5 months of age the hemoglobin was 10 Gm. after a blood transfusion. Dr. Hawkins, are you sure that she was transfused at that time? It is my impression that she was not. The average hemoglobin at that age is approximately 11 Gm., so that she really had not shown any unusual anemia prior to her present illness. Her first red blood count at Children's Hospital of 2.85 million also bears comment. A count done the day before was 4,300,000. The differential white blood count with 88 per cent lymphoblasts is certainly open to question. All previous and subsequent smears showed only

mature lymphocytes. In the differential diagnosis, some of the conditions that cause leucemoid reactions with lymphocytosis should be considered. Certain infections, such as pertussis, congenital lues, and chickenpox, are not infrequently associated with hyperleucocytosis with an absolute increase in lymphocytes. Leucemoid blood pictures are also seen in various intoxications, such as mercury or benzol poisoning. Of the malignancies that are sometimes associated with a leucemoid blood picture, Hodgkin's disease should be considered. The clinical picture is not out of keeping with such a diagnosis. However, in Hodgkin's disease there never is an absolute increase in the lymphocytes, and the bone marrow never shows an invasion with lymphocytes such as is seen in this case.

This is not a case of chronic or acute infectious lymphocytosis. Cases of chronic infectious lymphocytosis as described by Smith are characterized by prolonged upper respiratory infection with low-grade fever and minimal enlargement of the cervical lymph nodes. In Smith's nine cases, the counts range from 5,000 to 15,000, with some 35 to 80 per cent lymphocytes. Acute infectious lymphocytosis occurs most commonly without any signs or symptoms. There is hyperleucocytosis with 71 to 97 per cent lymphocytes. Within four to eight weeks, the blood picture is back to normal. Acute infectious mononucleosis can be excluded on many grounds. In infectious mononucleosis it is very rare for the leucocytes to exceed 40,000. This child has never shown an increase in the heterophile antibody titer, and at no time did the mononuclear cells suggest those typical of the disease. We now take into consideration the leucemias. Acute leucemia can be excluded in the absence of severe anemia, thrombocytopenia, and immature lymphocytes in the blood and bone marrow.

The prolonged course, the physical findings, and the laboratory studies are all in keeping with the diagnosis of chronic lymphoid leucemia. On careful analysis, all reports of chronic lymphoid leucemia in children actually represent cases of acute leucemia of prolonged duration. Chronic lymphoid leucemia, as it occurs in adults, has to my knowledge never been reported in children. It is difficult to explain the sudden onset of extreme pallor in this case. Severe progressive anemia is expected in the later stages of chronic leucemia. In the bone marrow studies, the erythroid elements are seen to be tremendously reduced, so that it is possible that the anemia is actually of long standing and had not been noticed by the parents. A better explanation of such a severe and sudden anemia would be an acute hemolytic crisis which is not unusual in cases of chronic lymphoid leucemia. The absence of reticulocytosis, elevated icterus index, and increased urinary urobilinogen are, however, against such an explanation.

Case 4. Uveitis

DR. JAMES CRAVENS.—This next case is that of a 9-year-old male who was admitted to Children's Hospital May 20, 1947. Except for one cold he had apparently been in good health all winter until April 18, when the mother first noticed that he had a mild inflammation of his left eye. There was red-

ness of the conjunctiva but he had no photophobia, lacrimation, or other complaints. There had been no previous injury to the eye, although approximately one week before the redness was noted the child had struck the left side of his forehead against an open storm window. This had caused a small bruise, but apparently the window had not struck the eye. Boric acid washes were applied to the eye for approximately one week with some improvement. On April 25, the mother noted that the left pupil was somewhat dilated. Three days later the patient was taken to an ophthalmologist, and treatment was begun. In the meantime a Wassermann, complete blood count, urinalysis, and tuberculin skin tests were all found to be normal. Several types of eye drops were applied, and the child was treated with hot applications and with three subcutaneous injections (substance unknown). During the first week of treatment he was free of subjective symptoms but three weeks ago noticed that vision in the left eye had failed. The only other symptoms present during this period were two mild headaches which the mother attributed to hunger, and a temperature elevation of 100° F. which occurred after a subcutaneous injection.

The past history of this case offers little relevant information. He was a full-term infant, delivered by instruments. There was no injury except for one small forceps mark on the head. The infant was breast fed for one month, then fed evaporated milk feedings, and later whole milk. He had chickenpox, measles, pertussis, and several attacks of otitis media and tonsillitis during the second year. When he was 3 years old his tonsils and adenoids were removed. Since that time he has had infrequent colds, and during the past six months has had only one cold, possibly a mild case of influenza which was followed by some nasal discharge from the right nostril for two or three weeks. He has been immunized against smallpox and diphtheria. He has had no contact with any contagious diseases. There is a history of a brief questionable exposure to tuberculosis. There are two siblings who are in good health. The father is in the Army in Japan at the present time and has been in good health except that he once had what the mother believes was retinitis. This was cured, and he has had no further ocular symptoms.

On admission to this hospital, the patient did not appear acutely ill. Abnormal findings were virtually limited to the eyes. On the right the pupil was round and regular and responded rapidly to light and accommodation. I could see nothing pathologic in the anterior chamber. The posterior chamber was clear, and the retina was well visualized. The disk and vessels appeared quite normal. On the left, the eyelid appeared puffy and there was some conjunctivitis and chemosis. The tension of the eyeball seemed slightly reduced to most examiners. The pupil was widely dilated and did not react either to light or accommodation. The cornea, the pupil, and anterior chamber, however, appeared quite clear. On ophthalmoscopic examination one could not get through to visualize the retina. There was a tannish-red cloudy medium throughout which appeared to be the vitreous, and in one portion of this I could see approximately ten or twenty pinpoint black bodies. The child is virtually sightless in this eye and could only tell me whether the ophthalmoscopic light

was on or off. The remainder of the physical examination revealed several palpable, small posterior cervical lymph nodes and one epitrochlear node which appeared to be round, smooth, and nontender. The pharynx was clean; the left nostril was injected and contained a small amount of pus. There was no sinus tenderness. At one time yesterday, May 22, it was noted that the child had somewhat exaggerated involuntary motions when he was sitting in bed. We could not definitely ascertain if this was due to nervousness, but no such movements have been seen since. The remainder of the physical findings were all negative. The hemoglobin was 13.9 Gm. There were 9,500 white blood cells with 2 eosinophiles, 1 juvenile, 1 stab cell, 54 segmented cells, and 42 lymphocytes. The red blood cells on the smear appeared normal, and the only unusual finding was occasional toxic granulation of the polymorphonuclear cells. The platelets appeared adequate. Sedimentation rate (corrected) was .325 mm. per minute. Typhoid 0 agglutination was obtained in 1:40 and 1:80, and it was negative in 1:160. All other agglutinations including typhoid H, paratyphoid, *Salmonella schottmülleri, Brucella abortus,* and proteus OX19 were negative. In addition, the tuberculin and Wassermann tests have been repeated but are not yet ready for report. The histoplasmin skin test is also being done at this time. We are obtaining x-ray of the chest, sinuses, and teeth.

DR. THEODORE SANDERS.—I believe this child is interesting from two points of view. The first one is the incidence of this disease in children, and the second one is the etiology. As far as the diagnosis goes, the ophthalmologists have a very great advantage because we have an organ we can look at, and our diagnosis is very often purely descriptive. In addition to the findings mentioned one can, with a slit lamp, see that on the endothelium there are a number of small keratitic precipitates which are agglutinations of white cells. The aqueous is cloudy. The vitreous is almost completely hazy, and with the ophthalmoscope a large number of stringy floaters which are agglutinations of white cells can be seen. I thought that I could see a white mass in the inferior part of the retina which might be a large area of choroiditis. I could not be sure of that at all.

Uveitis, of course, means an inflammation of the uveal tract, the uveal tract being the vascular coat of the eye—the iris, the ciliary body and the choroid. Anterior uveitis or iridocyclitis, in which the symptoms are chiefly in the anterior segment, can occur. There can also be a posterior choroiditis, or posterior uveitis and choroiditis. This case, I believe, is of the latter type. I believe that this is uveitis, but that most of the inflammatory process is in the posterior segment, which accounts for the marked loss of vision and the cloudy vitreous. Since the uveal tract is almost completely vascular, we believe that most uveal diseases are secondary to systemic diseases elsewhere. Search for an etiologic factor in these cases is usually futile. I don't think that the pediatrician appreciates this quite as much as the internist because of the rarity of these cases in children. Sometimes in the milder cases, we feel that it isn't even worth while to go through an intensive survey of the patient. The obvious etiologic factors, of course, are the chronic granulomatous types of inflammation, tuber-

culosis, syphilis, leprosy in some areas, sarcoid, and the like. I feel that in this country foci of infection are probably the chief cause. The mechanism of eye tuberculosis, I believe, is a hypersensitivity reaction and not a real tuberculosis with the tubercle in the eye. In other words, the child has childhood tuberculosis, and he develops an altered reactivity to the tubercle bacillus. Later, on further exposure, the vascular coat of his eye flares up. This probably happens seldom before adult life. I think one other factor must be considered here. A very small lesion in the choroid will produce a tremendous loss of vision, a physiologic loss which the patient notes as a very marked symptom. He will come to the ophthalmologist for a very tiny lesion in his choroid whereas if he had a similar lesion in a joint or in the cardiac muscle or elsewhere he would never know he had it. I think we see many minor lesions which would be passed up elsewhere. I think the slow evolution of the process accounts for the fact that we do not see much childhood tuberculosis of the eye. Syphilis of the eye shows up as keratitis. I believe that there is a very definite anterior uveitis associated with the keratitis. Possibly the anterior uveitis is the primary thing, and interstitial keratitis is only secondary to that. The interstitial keratitis is so much more obvious than the anterior uveitis that it is the usual clinical manifestation. It is difficult to incriminate foci of infection in any particular case of iritis. We can pull a man's teeth or we can take out his tonsils, and if he gets well that doesn't mean that we have eliminated the actual cause of the disease. I think that until we know more about this condition we're going to be up against a stone wall. It is important to try to discover the mechanism by which a focus of infection causes uveitis. Is it a septic embolus? I don't think so. Is it a bacterial allergy? Possibly. Is it some mechanism that we don't know much about, such as the Shwartzman phenomenon? Perhaps there is some unknown mechanism by which focal infection can cause a vascular tissue to become inflamed.

This brings us to a discussion of the management of these cases. Of course, the first thing we try to do is to eliminate the etiologic factor. This is actually the internist's, the dentist's, and the nose and throat man's job. As far as foci of infection go, I think teeth, sinuses, tonsils, and, in the adult male, the prostate are common sites. The gastrointestinal tract, I think, is less common, and there are probably other more obscure sites. The local treatment is important particularly in the anterior cases. Atropine is used to dilate the pupil. I think that is about the only local treatment that has any effect at all. Hot compresses may make the eye feel better, it is doubtful that they lessen inflammation. Foreign protein therapy, such as typhoid vaccine, constitutes the best treatment in the majority of cases. I think you all are aware that we do not know all that happens when typhoid vaccine is injected into an individual, but the response to typhoid in some of these cases is dramatic. I suspect that this boy will be getting foreign protein therapy before long. There's one thing here that might give us some hint as to the etiology in this case. This child has run a low grade fever; he has a slight leucocytosis; I suspect that he has a chronic

inflammation somewhere. In such a case the antibiotics may help, not by affecting the eye lesion directly but by curing the obscure infection.

DR. RUSSELL BLATTNER.—This condition is very rare. However, in February, 1941, we saw two children, brother and sister, 6 and 8 years of age, who had had mild chickenpox five weeks before. Both children recovered from this illness without complication and returned to school. About two weeks later the entire family, eleven in all, developed "flu." One week later both children developed photophobia, mild conjunctivitis, pain in the eyes, and gradual loss of vision. The children were brought to Children's Hospital. Severe bilateral uveitis was the diagnosis in both cases. Neither child appeared ill. The ophthalmologist, Dr. Scobee, concurred in the diagnosis. He performed bilateral paracenteses of the anterior chambers in each case. This material was inoculated on the chorioallantoic membrane of the fertile egg. Dr. Heys and I attempted to grow a virus or bacteria from this material but did not succeed. In addition to the surgical treatment, fever therapy was tried (Kettering hypertherm). It was the impression of the house staff that the local manifestations of uveitis were less marked, but vision was not improved. The girl was completely blind at the time of discharge. The boy gradually regained some vision, so that he could recognize objects across the room, and eventually recovered vision in the left eye, but vision in the right eye did not improve. Eighteen months later the boy developed a "cold." Signs and symptoms of uveitis recurred in the good eye. The patient was readmitted to the hospital. Because of chronic tonsillitis and maxillary sinusitis, tonsillectomy and adenoidectomy and antral washings were performed. Within a few days after this operation, vision in the left eye improved. The girl remained completely blind. We have not seen either of these children since the time of the second hospital admission.

DR. SANDERS.—A couple of months ago we showed five cases here: one of them was listed as iritis. You may remember, Dr. Blattner, that that patient had an herpetic ulcer with secondary iritis in which the iritis was probably herpetic, so that I should think it would fall in the same class as these. I think that the fact that virus was not recovered from the aqueous does not necessarily mean that there was no virus in the anterior uveal tract. I think Dr. Blattner's statement that the eye got better after tonsillectomy and again after hypertherm therapy illustrates one of our greatest difficulties in evaluating the etiology of the condition. Most of these cases improve if enough time elapses, no matter what therapy is instituted.

Case 5. Tracheo-esophageal Fistula

DR. JAMES COOPER.—The next patient is a 23-day-old infant admitted at the age of four days, with the diagnosis of tracheo-esophageal fistula. Instillation of small amounts of lipiodol into the upper esophagus revealed evidence of complete esophageal obstruction at the level of the manubrium sterni. The abdomen at the time was filled with air, so it could be assumed that a fistula was present. The infant was of premature size (2,340 Gm.), slightly dehydrated,

but with no evidence of infection. He was hydrated and placed on antibiotics, and the fistula was operated upon the following day. Two days following the repair of the fistula gastrostomy was done, and feedings were started via the gastrostomy tube. The postoperative course was uneventful except for periodic episodes of cyanosis until six days ago, when the child developed diarrhea on his thirteenth hospital day. Culture of the stomach contents at that time grew staphylococcus, diphtheroids, and *Escherichia coli*. The therapy of the diarrhea has been routine, and the diarrhea has not been too severe. At the present time diarrhea is abating, and the baby's condition is improving. The weight at present is 2,870 Gm. We have passed a ureteral catheter through the nostril into the stomach without any difficulty and then, in a retrograde fashion, established a gold-impregnated string in the esophagus for later dilatation.

Case 6. Tracheo-esophageal Fistula

DR. WILLIAM DAVIS.—This newborn infant entered the hospital May 20, 1947, at the age of 28 hours. The history of the pregnancy and delivery was not remarkable. In the nursery, it was noted that the baby became cyanotic and had a rattling respiration. This was relieved by frequent suction. The material suctioned at first was a light amber color not unlike amniotic fluid, and later it became clear and mucoid. Attempts to feed the baby glucose water on several occasions aggravated respiration and caused a great deal of distress. The water appeared to be regurgitated. Physical examination in this hospital revealed a well-developed 3,500 Gm. newborn infant with loud audible rhonchi heard without the stethoscope; the color was good and there was a good Moro reflex. There were a few moist râles at the bases of the lungs. Under fluoroscopy, an attempt was made to pass a tube into the stomach. At about the level of the cricopharyngeus muscle the catheter turned on itself, curled back, and passage beyond that point could not be made. There was some air in the stomach, but attempts to force this air up into the esophagus to visualize its distal segment failed. An attempt at operative repair of the fistula was unsuccessful. Postoperatively, the baby has been maintained on continuous intravenous alimentation in which a fat emulsion prepared by Dr. Rutledge is being utilized.

DR. MERL CARSON.—The condition of tracheo-esophageal fistula is one that we see rather infrequently here, and very fortunately. Several types of fistulas have been described, so that it might be wise to enumerate these very briefly. In one type the esophagus and trachea are both patent but are connected by a small fistulous tract. In a second type there is real atresia of the esophagus with no fistulous communication between the esophagus and trachea. The third type, which constitutes 75 to 80 per cent of the cases, is the type present in this child. There is a blind upper segment of the esophagus which is usually dilated and which extends down as a rule to the level of the fourth thoracic vertebra; extending upward from the stomach is the distal segment of the esophagus which narrows as it progresses upward and also ends in a

blind pouch. The portion between the two ends of the esophagus may be connected by small fibrous or muscular bands, or there may be no connection at all. The distance between these two segments may be quite wide (several centimeters), or it may be very narrow. In this type the fistulous tract usually runs from the lower segment of the esophagus directly into the trachea. More rarely it may connect to one or the other main bronchi, and more rarely still there may be a fistulous tract running from the upper portion of the esophagus to the trachea or to one of the main bronchi.

The clinical picture that is presented by these infants is as a rule quite characteristic, so that the diagnosis is easily established. Usually they are born in a normal manner, and examination of the infant immediately after birth reveals no evidence of abnormality. It is only after the first few hours in the nursery that one begins to suspect trouble. Initially, the nurse will comment on the fact that the child has a large amount of mucus in his throat, that she continually has to suction it out. He breathes noisily and occasionally will choke and cough, so that very frequently the infant's nurse will be the first to suspect the diagnosis. At the time the child is fed, the characteristic symptomatology appears with the first few swallows of water. The child does well, but as the feeding continues, he will regurgitate the fluid, and it may be aspirated, producing choking, cyanosis, and sometimes unconsciousness for a period. Suction and oxygen administration must be used to revive him. Abdominal distension, which is unusual in a child this age, is often striking. The distension is usually in the upper portion of the abdomen, and on fluoroscopy most of the air is seen in the stomach, whereas the lower portion of the abdomen and the intestinal tract is not filled with air during this early period. The regurgitated material does not contain bile. The meconium that is passed by these children is characteristic in that it contains no epithelial cells in keeping with the findings obtained in atresia anywhere in the gastrointestinal tract. The diagnosis suggested by these clinical observations can easily be confirmed by the use of a catheter which is passed into the esophagus and which is seen to progress to the end of the blind sac and then curl back up. If one wishes to employ opaque material, lipiodol should be used rather than barium, since any material put into the upper pouch of the esophagus invariably will be regurgitated into the pharynx, and a portion of it will be immediately aspirated. Barium is extremely irritating to the lungs and initiates a fulminating pneumonia.

In the medical treatment of these patients one is primarily concerned with the prevention or treatment of pneumonia which develops as a result both of aspiration of the regurgitated contents of the esophagus and as a result of regurgitation of the stomach contents directly into the bronchial tree through the fistulous tract. Prevention of pneumonia is best accomplished by early surgery, by omitting oral feedings after diagnosis has been established, and by not using irritating opaque media in the esophagus. The other point that is of extreme importance in the medical management is the establishment and maintenance of optimum nutrition. If surgery can be instituted early, nutrition usually can be well maintained by feeding through a gastrostomy opening.

DR. THOMAS BURFORD.—Surgery of esophageal atresia and tracheo-esophageal fistulas has intrigued pediatric surgeons for a long time. Formerly, an occasional patient was salvaged by the long hard method of swinging out a proximal flap of the esophagus into the neck and then doing reconstructive tube procedures connecting this proximal loop of the esophagus with the stomach. The procedure was not a good one, and the number of patients who had the good fortune and the number of surgeons who had the fortitude to pull through the long procedure that was necessary were few indeed. In 1933, Dr. Cameron Haight was able to report the first successful end-to-end anastomosis in a case which was of the more common type with a blind proximal loop and a distal loop connected to the trachea. It is fortunate that that is the form usually seen, since there is very little that can be done to or for the other types. It is a simple enough matter, however, to do an anastomosis between the blind proximal loop and the freed distal segment. The failures will result from there being too much tension on the suture line. That will stem from too much separation initially between the two loops. It is significant, I think, that we have learned to operate on these people. We have had four cases and four operative survivals. Unfortunately, we have encountered two in this group for which nothing could be done. They were not of the type amenable to surgery. The last baby shown today (Case 6) had a complicated dual tracheo-esophageal fistula with a long atretic segment between the proximal and distal ends of the esophagus. There was no possibility of bringing the two ends together for an anastomosis. Two of the cases have been of the type which can be repaired. In the first case the ends were rather widely separated, and the suture line broke down. The child died of complications of the esophageal disruption. The other case (Case 5) was ideal in that it was of the common type, and the proximal and distal loops were close enough to allow an end-to-end suture without too much tension on the suture line.

I return to emphasize that we do know how to operate on these children, and I think whenever the proper anatomic situation is found at operation, we should get a good result by performing an end-to-end anastomosis. Some, such as this child (Case 5), will require subsequent dilatations, but in the experience of Ladd and Swenson, who have now had some seventeen or eighteen patients, they dilate readily and apparently require few subsequent dilatations because the stricture which develops is very narrow.

DR. ALEXIS HARTMANN.—It is too late in the morning to go into the details of parenteral feeding. I merely want to restate what the problem is and about where we are in its solution. Prior to this conference, whenever we presented this problem we tried to solve it without consideration of the possibility of administering fat, and we always concluded as follows: we should be able to give complete parenteral feeding from a qualitative standpoint without too much difficulty with the use of Amigen, dextrose, plasma (especially enriched plasma), vitamins, and properly chosen salts. We should be able to supply the right amount of water which might be about 200 c.c. per kilogram,

the right amount of minerals in a balanced form, some 3 to 5 Gm. of protein or potential protein per kilogram per day, and possibly 10 to 12 Gm. glucose per kilogram per day, and all of the fat-soluble and water-soluble vitamins known. From a quantitative point of view, however, except perhaps for a few days when dehydration is present, which would allow for an unusual water administration, we could scarcely get beyond half of the desired caloric intake, and we would wind up with about 50 or 60 calories per kilogram body weight unless we gave so much fluid to get further calories in that it caused water-logging. Today, Dr. Rutledge has some fat emulsified by a new principle, a principle which attempts to avoid the toxicity of lecithin which previously has been used as the emulsifying agent and which has been a stumbling block in that it is difficult to procure and in that lecithin is toxic and deteriorates rapidly. With this fat emulsion, which, it seems, can be administered without reaction, it ought not to be difficult to add another 30 or 40 calories per kilogram of body weight per day, so that we ought to be able to get up to about 80 calories per kilogram and perhaps even to 100 without the risk of water-logging. Perhaps at a subsequent conference when the occasion permits, we can work this out on the blackboard to demonstrate the details of parenteral alimentation.

DR. ROBERT RUTLEDGE.—This emulsion consists of 10 per cent fat. It does not require any complicated apparatus (it is made in an electric cocktail mixer), and it does not break down after it is autoclaved.

DR. BLATTNER.—What is the globule size, Dr. Rutledge, compared with regular milk, homogenized milk, and breast milk?

DR. RUTLEDGE.—By comparing roughly the particles of the emulsion with red cells, it is about one-half the diameter of the red cell (3 to 4 microns). Those are the largest sized particles; then there are a great many particles much smaller, and some almost submicroscopic which can be seen as a little occasional flash of light in the dark field. It is interesting that the chyle from the cases of chylothorax has particles in it that are sometimes as large as 15 to 20 microns in diameter, and yet it does not seem to cause a lot of trouble.

DR. HARTMANN.—Several times the diameter of red cells.

DR. RUTLEDGE.—That is a very interesting point, because while many emulsions have been made with extremely small particle sizes in large, high-pressure, homogenizing machines, they always seem to get stuck up in the lung, in the liver, and in the reticulo-endothelial system. Red cells and large white cells seem to slide through capillaries without any trouble, and this makes one surmise that the important thing is not the size of the particle but its chemical and physical properties.

DR. HARTMANN.—I meant to mention before that as a basic feeding for this second child we should give about twice daily, therefore about every twelve hours, 50 c.c. per kilogram body weight of the D.A.S.* solution which we have

*Dextrose 10 per cent, Amigen 10 per cent, and special salt mixture in equal parts.

been using when first feeding babies with diarrhea after the initial period of food restriction. That amounts to 3.3 per cent dextrose and 3.3 per cent Amigen. The mineral composition has been changed by the special salt mixture, so that if one, for instance, were able to get 180 c.c. per kilogram of the D.A.S. solution into the baby, he would be receiving almost exactly the mineral that he would be getting if he were taking 100 calories per kilogram in the form of human milk. That was the basis for the particular construction of the salt mixture: to get in sodium, potassium, calcium, magnesium, and chloride in the proportion and amounts that a breast-fed baby would be getting them. If you got in just 100 c.c. instead of 180 c.c., it would be somewhat short in mineral but perhaps would be an adequate amount, since even the breast-fed baby does not have the retention of minerals that would match his intake, and, of course, the discrepancy is much greater in cases of a baby fed cow's milk where the intakes are very much greater than the retention. I imagine that if the baby got 100 c.c. per kilogram, it would still be adequate for retention purposes. If we followed these subcutaneous injections of D.A.S. with 10 per cent glucose intravenously and followed or preceded that with administration of the fat emulsion (20 c.c. per kilogram), and then gave parenteral vitamins in the usual way, we would be giving 80 calories per kilogram, up to about 4 Gm. protein per kilogram, and up to 12 Gm. carbohydrate per kilogram with an appreciable amount of fat. The next thing, I think, that we should look into to make it simpler from a technical point of view would be to see, Dr. Rutledge, whether we could incorporate in the fat emulsion the fat-soluble vitamins, so that we could avoid repeated intramuscular injections of vitamin preparations. With any of the intravenous or subcutaneous injections it would be a simple matter to add the water-soluble vitamins, so that fewer separate injections would be needed.

DR. DAVIS.—Dr. Hartmann, would you suggest that with the continuous intravenous drip, we switch flasks from the D.A.S. to glucose?

DR. HARTMANN.—Yes, I think that if you are successful in establishing a continuous intravenous drip, you should take full advantage of the situation, and pass from one to another. You could administer fat, and when it is practically all in, wash the rest of it in with the glucose or with a plasma transfusion and go on in that manner.

DR. HARRY LAWLER.—Once the continuous intravenous drip is in place, it is not necessary to restrict the intake to such limited quantities as those mentioned in your discussion, since high concentrations of Amigen and glucose may be given without danger. High concentrations of these substances may also be given subcutaneously in selected cases.

DR. HARTMANN.—Yes, that is true. What we have worked out was for all babies. Something was needed that would not cause irritation under any circumstances. Of course, you know for a fact that you are not going to be able to use the intravenous route indefinitely in this baby. Technical difficulties

will certainly crop up, and I think it would be worth while to make your basic procedure utilize subcutaneous administration for most of the water that you are going to have to give, so that you can save veins for the things, that must be given intravenously, such as fat.

DR. LAWLER.—Can fat emulsion be picked up from the peritoneum?

DR. RUTLEDGE.—We have not done very much about that.

DR. HARTMANN.—That is certainly something that has to be thought of later, whether subcutaneous and peritoneal administration can be utilized. These might be successful. It is amazing what is picked up from the peritoneum. Actual intact red cells get through and into the circulation. It is possible to inject avian blood with nucleated corpuscles intraperitoneally and find these cells almost immediately in the general circulation.

REFERENCES

1. Pratt, J. P., and Shaefer, Robert L.: Sex Precocity, Virilism, Adrenal Cortical Tumors, Am. J. Obst. & Gynec. **49**: 623-633, 1945.
2. Novak, E.: The Constitutional Type of Female Precocious Puberty With a Report of Nine Cases, Am. J. Obst. & Gynec. **47**: 20-42, 1944.

The Social Aspects of Medicine

THE SOCIAL ASPECTS OF MEDICINE: A STATEMENT

JOSEPH PALMA, M.D., F.A.A.P.
(Chairman for Hawaii)

I was interested to note in the April, 1947, Vol. 30, No. 4, JOURNAL OF PEDIATRICS, an article on compulsory prepaid medical care by one Dr. Ernst P. Boas, Chairman of the Physicians' Forum. I think this is in keeping with the democratic principle of hearing from the proponents as well as the opponents of compulsory prepaid medical care which is also euphoniously called organized prepayment," also "compulsory medical insurance," all of which is only a play on the music of words because this scheme, aimed at regimentation of not only the profession but of all the people, is in reality a compulsory sickness tax.

In the future, I would suggest that all writers on this subject, either for or against, offer some documentary evidence as to who they are and whom they front for. As an absolute *must* on the list of reading on this subject, all physicians should avail themselves of the pamphlet "Blueprint for the Nationalization of Medicine," by Marjorie Shearon, Ph.D., Post Office Box 4034, Chevy Chase 15, Maryland. Single copies can be obtained for twenty-five cents and I know of no better investment in education, especially for such a trifling sum. Other reading on this must-list and a virtual textbok on the subject is, "Compulsion, the Key to Collectivism," published by the National Physicians' Committee for the Extension of Medical Services, Inc., 75 East Wacker Drive, Chicago, Illinois.

Any attempt to answer in detail, or point by point, the specious arguments advanced by Dr. Boas and others of like ilk of the professional do-gooders and fellow travelers, is a mistake and a waste of time. The primary concern of all of us is a matter of principle, the preservation of the present high standards of medical care, and the preservation of liberty in this freedom loving land. The cornerstone of our great system of American medicine—the best that the world has yet produced under any system—is the maintenance of the sacred patient-and-doctor relationship. No government, no bureaucrat, no third party must ever be allowed to intrude into this most intimate and personal relationship. The proponents of compulsory prepaid medical care by government taxation would take us on the first step on the road to statism, collectivism, totalitarianism, communism, or whatever term you wish to apply to the foreign ideology which is in opposition to the American way of life.

In answer to the suggestion in Dr. Palmer's letter for information concerning Dr. Ernst Boas I give the following from Vol. 24, 1946-1947, Who's Who in America.

> Ernst Philip Boas, born February 4, 1891. B.S. Columbia, 1910, M.A. 1912, M.D. 1914, Instructor in Pathology, College of Physicians and Surgeons (Columbia), 1917, Instructor in Physiology, 1920-21; Medical Director Montefiore Hospital, 1921-29. Post-graduate teacher, diseases of the heart, Columbia, since 1926; Assistant Clinical Professor of Medicine since 1928; Associate Editor Modern Hospital, 1923-29; attending physician Montefiore Hospital, 1929-30, Associate physician, Mt. Sinai Hospital. Capt. Med. R.C. 1917-19, Chief of Medical Service, Base Hospital 63, A.E.F., Chairman, Physicians Forum for Study of Medical Care. Fellow A.M.A.; Mem. Soc. for Clin. Investigation, Harvey Society, New York Academy Medicine, New York Tuberculosis and Health Assn. (dir.; chmn. heart com. 1933-42). Phi Beta Kappa, Alpha Omega Alpha. Author: The Challenge of Chronic Diseases, 1929; The Heart Rate, 1932; The Unseen Plague Chronic

Diseases, 1940; Treatment of the Patient Past Fifty, 1941 (2nd edition 1944). Writer on diseases of heart and chronic disease as a community problem.
Address 1185 Park Avenue, New York, New York.

I might add that Dr. Boas is the son of the famous anthropologist, Dr. Franz Boas of Columbia University.

E. A. P.

AN OPEN LETTER TO DR. PALMA:

I have read Mr. Milliman's* intelligent (and adverse) criticisms of compulsory prepaid medical care as proposed in the Wagner-Murray-Dingell Bill S.1606. I have read Dr. Ernst P. Boas' equally intelligent reply to it.† And now I have read your reply to Dr. Boas, which you have sent to the state chairmen of the Academy. In this open letter to you, I am sure you will understand that although I am State Co-Chairman for Missouri, my comments on your statement represent my own opinions and *not* those of any of the Missouri Fellows.

Freedom of speech and press is part of true Americanism, an opinion which I am sure Dr. E. A. Park, who conducts the JOURNAL'S column on the "Social Aspects of Medicine," shares with both you and me. I have no doubt that he will publish your statement and possibly various comments thereupon.

I had hoped that your statement would continue the cool, scientific attitude of the two communications which evoked or provoked it. But your request for "documentary evidence of who they (writers on this subject) are and whom they front for," and your "specious arguments advanced by Dr. Boas and others of like ilk of the professional do-gooders and fellow travelers," suggest a reaction of hyperpyrexia on your part. And so it is with many physicians, so volubly and expensively represented by the National Physicians' Committee for the Extension of Medical Services, crying "Come weal, come woe, my status is quo!"‡

Here, Dr. Palma, is the gist of the matter: Are you correct in saying that American medicine is the best the world has produced under any system? Some (not all) of the New Zealanders, Danes, and Swedes would voice firm and documented disagreement. More important, let me quote one, perhaps omitted from your list of heroes, Franklin Roosevelt:§

> "We have reason to derive great satisfaction from the increase in the average length of life in our country and from the improvement in the average levels of health and well-being. Yet these improvements in the averages are cold comfort to the millions of our people whose security in health and survival is still as limited as was that of the nation as a whole fifty years ago."

For my part, I am convinced, as are you, that a third party should not intrude *medically* between doctor and patient. But spreading the cost of medical care by the insurance method need not involve this. If machine politics cannot be kept out of medicine, then woe betide doctor and patient! The current version of the Wagner-Murray Dingell bill endeavors, by decentralization, to avert such political control. At present, on this matter of "means-to-a-better-end," I am in the position of a confused liberal, and have so told my class in professional conduct and economics.

But it must be clear to all not overcome by Red-baiting fever (Rubrophobia?) that American medicine produces remarkably well what it distributes amazingly ill. Only insurance can properly help our patients pay for this expensive essential. And only *more* physicians, more of the despised do-gooders, can purvey the best medical care to those who need it most and have it least.

(Signed) PARK J. WHITE, M.D.
St. Louis, Mo.

---

*Milliman, W. A., J. PEDIAT. 29: 527, 1946.
†Boas, Ernst P., J. PEDIAT. 30: 478, 1947.
‡Quote seen in the *Atlantic Monthly* some years ago.
§Message on Health Security, July, 1938.

My dear Dr. Park:

I am submitting the enclosed manuscript for consideration of publication in the very interesting "Social Aspects of Medicine" column in the JOURNAL OF PEDIATRICS. The rapid growth of these cooperative ventures and the response with which they are meeting, indicate a widespread interest among the lay public in such enterprises, and it should help to round out the picture you are presenting in the JOURNAL. There are a thousand families already enrolled in the group here, in spite of a medical service bureau, Blue Cross, and at least five commercial insurance plans.

It is, of course, my hope that you will see fit to publish this paper, for we are genuinely interested in progressive medical measures and would welcome the comments it would stimulate. Our plan is flexible and we not only wish to improve it but to make it acceptable to the medical profession.

(Signed) W. A. MACCOLL, M.D.

THE GROUP HEALTH COOPERATIVE OF PUGET SOUND

WILLIAM A. MACCOLL, M.D.

Interest in the social aspects of the practice of medicine is not limited to physicians. The greatest concern belongs to the consumer group whose lives, in number, are far more extensively involved. A common meeting ground of these interests lies in the various Group Health Cooperative plans formed, forming, or in the planning. It should be of interest to readers of this department to have a report on the operation of one of these, together with the principles underlying the organization.

The Group Health Cooperative of Puget Sound, Seattle, Wash., has been established by physicians and laymen in concert, and may serve as a prototype for similar organizations. This clinic has been in operation for six months as a Cooperative, but the group of physicians had been conducting an industrial contract practice for twelve years previously, and continue to do so in the present transition period.* The Cooperative plan has not yet been recognized by the local medical society or the American Medical Association, although data on all phases of its operation have been submitted to the latter for study. It is the conviction of those immediately concerned that this form of provision for medical care is ethical, worthy, meets the needs of physician and consumer, and will, if allowed to develop sufficiently, limit the need for any extensive federal intervention in the distribution of medical care either in urban or in rural areas. For this ideal, at any rate, the physicians have given up their memberships in the medical societies and stand relatively alone in what they believe to be a forward step in the progress of American medicine.

A description of a Cooperative and an outline of its functions as a group health organization will clarify subsequent discussion. The American Cooperatives are founded upon the Rochdale Cooperative principles, expressed by the five points:

1. Open membership: no discrimination on the basis of race, sex, creed, or economic status.
2. Fairness and equal rights for all.
3. Democratic control: one member, one vote.
4. Not for profit but for service.
5. The users thereof profit thereby.

Family Membership in a Group Health Cooperative is through subscription of an initial investment in the capital assets of the Cooperative. The membership fee in the present case is $100.00, payable over a twenty-month period. This sum is returnable in full should the member leave the service area, or may be willed at death. The membership funds are used to provide the buildings and equipment for the organization and are not employed for operative purposes.

A Board of Trustees, elected by the members from their number, manages the business affairs of the organization, and may appoint committees to assist them. The board meets

*Private patients are also seen, all fees going to the central fund.

with the Medical Director (a physician) and the Chief of Staff on all administrative problems relative to the practice of medicine. The Service Contracts, Staff Contract, and Staff Organization are outlined below.

The Group Health Cooperative is in principle and practice a democratic nonprofit, medical service organization.

Services are provided for the entire family on a dues-paying basis. An abstract of the service agreement is as follows:

1. Medical and surgical care in the home, hospital or office, including preventive measures.

2. Diagnostic x-ray examinations of all kinds, including dental.

3. Physical therapy as prescribed by the physicians.

4. Laboratory tests and procedures as indicated by the physicians.

5. Drugs, medicines, and surgical supplies as prescribed, except orthopedic or corrective devices, prostheses, visual aids, vitamins, hormones, blood plasma, radium or deep x-ray therapy.

6. Prophylaxes against those diseases which are preventable by appropriate inoculation.

7. Dental care is not at present provided, but is projected.

8. Emergency care up to $50.00, including ambulance service when necessary.

9. Hospital care in ward beds, unless ordered otherwise by the physician (except cases subject to quarantine regulations) up to 180 days for each illness. Special nursing is available when ordered by the attending physician.

10. Exclusions: cases covered by Federal or State law, insanity, tuberculosis, venereal diseases, mental disorders, alcoholism, drug addiction, attempted suicide. Pre-existing conditions noted in the contract, obstetric care within ten months of membership, tonsillectomy within six months, and surgery other than emergency within three months are cared for on a cost basis where the member is in good standing. The Cooperative will diagnose the conditions and will treat venereal disease in the acute infectious stages.

11. Members and their dependents will comply with all the recommendations of the attending physicians and "failure to do so shall automatically terminate all rights to any further services and benefits hereunder."

This is believed to be one of the most inclusive medical care programs in the country, assuring the family complete coverage, for all members, for the vast majority of their ills on a self-supporting, budgeted basis. The current dues are $3.00 per month per adult and $1.50 per child per month, the first two children only being charged. In order to receive service after the age of 65, a member must have held a continuous membership for five years.

Dues of $108.00 per year for a family of four is not beyond the reach of a working family in this area of high wages and high living costs, when one considers that the coverage is complete with no additional cost for medicines, fees for "first visits" or the other numerous extra charges found in many contracts. Many wage earners find that over a period of years their average annual medical costs have been considerably higher, and it is difficult for some to believe that they are not going to receive a "cut rate" type of care. The dues are, however, above the means of the indigent, the unemployable, or the old-age pensioner. Some form of Federal or State aid is necessary for their care. The standards and organization of the Group Health Cooperative would be adaptable to a State aid program on a contract basis. The clerical load could be centralized and the medical care supervised by the Medical Director and Chief of Staff. As Dr. Boas has recently pointed out in this column (30: 481), "It has become a truism that the best medical care is given by physicians cooperating in a well-knit group, the services of the group being purchased not by a fee paid for every service but by a prepayment plan."

The Medical Staff is composed of general practitioners and specialists, working under the direction of the chief of staff elected by the members of the staff and agreed to by the board of trustees of the Cooperative. The staff works on a contract with the Cooperative, which is abstracted as follows:

1. The Cooperative recognizes the staff as bargaining agency for its members, and will entrust to the staff all matters of maintenance of standards and the regulation of medical

practice by its members. "The Cooperative shall not supervise, regulate or intervene in, the professional relationship between any physician and his patients."

2. The staff shall consist of the physicians employed by the Cooperative and the Chief of Laboratory. Each member of the staff shall have one vote in the business of the staff, and the staff shall adopts its own by-laws, which, among other things, shall:

A. Define procedures to be followed in diagnosis and treatment to the end that all staff members will comply with standards obtaining currently in the leading medical institutions of the country.

B. Define the scope of practice of each specialty.

C. Define the duties of each department of the staff.

D. Make provision for regular meetings of the staff for educational and professional purposes, and for the maintenance of the highest standards of practice.

E. Make provision for the election and removal of the chief of staff or of any member of the staff.

3. Staff members shall give their full time to the performance of their duties for the Cooperative, except for such teaching as may be desired.

4. No physician shall be employed by the Cooperative who is not:

A. Licensed to practice medicine in the State of Washington;

B. A graduate of a school accepted as Grade A at the time of his graduation;

C. Acceptable to the rest of the staff by a two-thirds vote by secret ballot;

D. No physician will be employed as a specialist unless he has had at least the training required by the examining board in his specialty.

5. The chief of staff shall be elected by the staff to serve for three years, subject to re-election. If not re-elected, he may continue to serve on the staff. His duties shall include:

A. Enforcement of all regulations of the staff including those relating to the standards of treatment and care;

B. Recommendation to the staff of measures designed to effectuate constant improvement in the standards of care and service;

C. Performance of such other duties as may be assigned in the by-laws of the staff.

6. The Cooperative will set up a retirement trust fund for each staff member, contributing one-half the required amount to assure $25,000.00 as a retirement benefit.

7. Dismissal from the staff will be the result of any unethical conduct as defined in the Code of Ethics of the A.M.A. or for refusal to cooperate with the other members of the staff in the performance of his duties, or for violation of the by-laws of the staff or the contract. Dismissal for these causes will be determined by the staff at a fair hearing. If the Cooperative dismisses a physician for any reason other than retirement at 65 years or cause. they shall pay him six months' salary as liquidated damages.

8. The chief of staff shall submit to the Cooperative annually a budget for salaries, said monies to be divided by the staff in accordance with their own wishes. Fifty per cent of any profits in a given year shall be returned to the staff for bonus distribution, the remaining half to be used for research funds, equipment, and improvements in plant and facilities.

The physicians' salaries range from $500 to $1,000 per month, with a definite program of increase on an annual basis. These figures are comparable to the income of a private practitioner grossing $12,000 to $18,000 annually. All expenses for equipment, supplies, facilities and personnel are met by the organization. The salaries quoted are net figures, giving the physician a dependable, assured income irrespective of good or bad months, uncollected bills, etc. A group accident and health policy is carried by the clinic for the physicians, and physicians are entitled, free, to all the medical coverage of a Cooperative member.

The Staff By-Laws are consistent with the contract abstracted above, with provisions for the regular educational and professional meetings of the staff, the maintenance of professional standards, required postgraduate study, ethical behavior, functions of various committees, and the management of their own affairs. Standards of treatment are described as those prevailing at the best teaching institutions and published in the standard reference works in the various fields of medicine and surgery.

The rights of the staff are fully protected. There is no interference in the practice of medicine nor in the patient-physician relationship; no layman makes any profit out of the labor of the physician, and the medical affairs are managed entirely by the staff of physicians and the medical director (also a physician) who is the liaison between the staff and the board. It has been stated repeatedly that a contract practice is discouraging or at least not conducive to continued study and development of the physician. This is without foundation. There is no stimulus more strong than the pride in and pressure of a group of physicians working as closely together as such a staff must work. The work of any individual is under the constant scrutiny of his fellows, and the standards are those of the best of the group rather than of one individual working in an isolated office.

The Philosophy of Group Practice is constantly emphasized, in that no man is required to care for those conditions for which he is not specifically trained, that the individual physician is part of the team, that the best interest of the patient is served only if the best care is provided by the whole group, and that the responsibility for the care of the family is a joint responsibility. Duplication of tests and x-rays is eliminated, and there is a continuous record on the patient containing all the information collected over the entire period of the individual member's service. The advantages of group practice to the physician and the patient are well recognized and need no further comment. When a condition arises for which the staff members are not competent to treat, the patient is referred to a local specialist, and the bill is paid by the clinic.

The application of group practice within the structure of a Group Health Cooperative results in many additional gains for physician and patient. The democratic participation of both members and staff stimulates mutual faith and understanding. The fact that the venture is a joint one in which both have high stakes tends to limit abuse on either side. These intangible advantages remove the elements of fear of the physician, distrust of procedures, and much of the anxiety relative to medical insecurity.

The patient-physician relationship is closer than in many other situations. The sixteen physicians in the present group are spoken of as "our doctors" by the members and are known to the entire family. When a new crisis arises, the specialist comes to the patient as an old friend of the family rather than someone "called in" for the occasion. The staff member is part of a medical family, just as the patient is part of a domestic unit. Free choice of physician is exercised by choice of the group, since membership is voluntary, but the staff is sufficiently large to permit leeway for individual tastes and preferences. Since a high value is placed on the general practitioner he frequently becomes the preferred member and refers to specialization such problems as are of an appropriate nature. This leaves the specialist free to concentrate more closely on his specialty.

In such an organization, the control and financial burden are spread so widely throughout the membership, and the lines of authority and management are so democratic, that no special interests or groups can exert undue influence. The practice of medicine is placed on an ideal plane, free from economic, social or political pressures, so that the personal and scientific aspects are left paramount. The patient is cared for purely on the basis of the best medical judgment in the individual case.

The nonprofit aspect of the Cooperative assures the patient of maximum service for his fee and an adequate return for his money. Too large a profit over a period of time would result in lowered rates, removal of exclusions, or increased services in other fields. The removal of the profit element repersents a great social advance.

The close contact with members and the absence of economic barriers to care provide an ideal basis for a fully applied preventive medicine program for the entire family. This is particularly valuable to the pediatrician who can, through immunization, periodic physical and psychological inventory, and knowledge of other illnesses and crises in the family, guide the parents toward better child management. Family problems are dealt with on a staff basis, which is of inestimable value to the pediatrician.

The physician has complete freedom of function within the limits of good medicine. Opportunity for research, postgraduate training, rest, relaxation, and "the good life" are

recognized by the Cooperative as desirable human rights and are provided for in the planning on the thesis that the best physician is the healthy and happy one. No limitations as to number of patients, laboratory facilities or procedures are placed upon him. So long as he continues to play his part in the integrated organization of the staff, his position is secure and he may practice in an unobstructed field.

Cooperative medicine is not in the ordinary sense competitive, since the patients are allied to the group through a parallel interest. The worst features of competition in the practice of medicine are eliminated. But the desire to produce the best, to establish a local reputation for sound practice and to contribute to the group, the community, and the profession are all retained. There is no temptation to stoop to the attractive, bizarre, and the spectacular practices which have arisen from time to time in medicine and have done so much to raise the cost of care and lower public confidence in the profession.

The educational program possible in a Cooperative is one which is of unusual value. The constant publication of material on maintenance of good health, of special articles written by the staff for the members, of information relative to current and anticipated epidemics, all these are of aid in carrying out the prevention program. The greater the success of the preventive measures, the healthier the patients, the lower the cost of care, and the less the burden for the physician. To the pediatrician, the educational feature is one of the greatest challenges of his position. Able to keep the parents informed on all matters of child care and training, on growth and development, on all matters of health from the prenatal to the adolescent, he has an unequaled opportunity to present to his fellows at "graduation" a group of physically and mentally sound individuals who are ready and able to take their places as productive citizens in the community.

At the present time, the Group Health Cooperative of Puget Sound is operating one large central clinic and its own hospital. As the membership grows and the numbers increase in outlying areas, it is projected that medical offices of suitable size will be installed, manned by well-trained general practitioners on an approximate ratio of one physician to 500 families. These units may include infirmaries for minor surgery and lesser illnesses. Diagnostic problems, cases requiring specialized care or treatment, and all major surgery will be referred to the central unit. The specialists from the central clinic will make rounds of these centers periodically to hold diagnostic and teaching clinics for the dual purpose of educating the practitioners in the specialty developments of medicine, and in aiding in the care of the patients on a local level, bringing urban medicine to the rural areas. The local physician will hold full staff membership in the central organization, attending staff meetings, rotating night duties with his neighbors, and enjoying many of the advantages of the group.

This program has the backing of the State Grange, labor organizations, civic groups, and the Cooperative League of the U. S. A.

The above report is presented as a practical method of solving a major problem in medical care distribution. It represents a prepayment, insurance-based, consumer-owned but professionally conducted method of supplying the best practical medical care to a wide service area in a manner which will not only apply medical knowledge efficiently but provide for the most economical and profitable use of the trained physician and surgeon.

News and Notes

At the Fifty-Seventh Annual Meeting of the **American Pediatric Society**, held at Stockbridge, Mass., May 13 to 15, 1947, the following officers were elected for 1947-48:

President, Dr. Grover F. Powers, New Haven
Vice-President, Dr. Harold B. Cushing, Montreal
Secretary and Treasurer, Dr. Henry G. Poncher, Chicago
Member of Council, Dr. James L. Wilson, Ann Arbor

The following were elected to membership: Drs. Dorothy Anderson, John A. Anderson, Richard L. Day, Harry J. Ebbs, Katherine Bain, Samuel Rapoport, Albert D. Kaiser, Murray H. Bass, Elvira Goettsch, Ralph V. Platou, Edith L. Potter and Robert Ward.

At the recent meeting of the **Society for Pediatric Research**, the following officers were elected for 1947-48:

President, Dr. Donovan J. McCune, New York
Vice-President, Dr. Sidney Farber, Boston
Secretary-Treasurer, Dr. Robert Ward, New York

The Harvard Medical School has announced an intensive graduate course in pediatrics to be held at the Massachusetts General Hospital, Boston, Oct. 13 to 24, 1947. The course will run six hours daily for two weeks and will include diagnosis, therapy, and prevention of diseases of infants, children, and adolescents with emphasis on recent advances. For further information write: Course for Graduates, Harvard Medical School, Boston, Mass.

Dr. Dwain N. Walcher, instructor of pediatrics at Yale Medical School, has been appointed to a newly created position of Assistant Professor of Pediatrics at the Indiana University School of Medicine at Bloomington.

Hospital bills, salaries for physical therapeutists, nurses, and other charges which may be essential to good medical care for patients with poliomyelitis, may be paid for by the chapters of the **National Foundation for Infantile Paralysis**. The nearest local chapter should be contacted for aid to patients in need of financial assistance to meet the cost of good medical care. The funds available for this purpose come from the March of Dimes.

In the first quarter of 1947, approximately 973,000 births were registered in the United States, according to preliminary estimates released by the National Office of Vital Statistics, U. S. Public Health Service, Federal Security Agency. This is 46.5 per cent more than the 664,000 births estimated to have been registered in the first three months of 1946, and it is 29 per cent more than the number recorded in the first quarter of 1943, the year which held the record for births until outstripped by 1946.

The following have been certified by the **American Board of Pediatrics**:

CANDIDATES EXAMINED IN CHICAGO, APRIL 25, 26, AND 27, 1947

Irving R. Abrams, 6740 North Sheridan Road, Chicago, Ill.
Cornelius Benton Burns, 57 South Broughton Street, Orangeburg, S. C.

Beach M. Chenoweth, Jr., 620 South 20th Street, Birmingham, Ala.
Robert Cohen, 4063 Radford Avenue, North Hollywood, Calif.
James A. Conner, 5307 Hyde Park Boulevard, Chicago, Ill.
LaMeta Frances Dahl, 4200 East 9th Street, Denver, Colo.
Joseph K. David, Jr., 411-12 Professional Building, Jacksonville, Fla.
Gerti Dooneief, 687 Montgomery Street, Brooklyn, N. Y.
Richard E. Dukes, 602 West University Avenue, Urbana, Ill.
Aaron Robinson Edwards, 2315 Parkwood, Pittsfield Village, Ann Arbor, Mich.
James Nickolas Etteldorf, 376 South Bellevue, Memphis, Tenn.
Donald G. Evans, 205 Stimson Building, Seattle, Wash.
Elizabeth Gentry, Maternity and Child Health Division, Texas State Health Department, Austin, Texas
Joseph R. Goran, 1035 East 19th Avenue, Denver, Colo.
Walter A. Goss, Jr., 602 Mayer Building, Portland, Ore.
George Wainwright Griffin, 2501 North 16th Avenue, Birmingham, Ala.
Wesley Robert Heard, 1417 Wilson Avenue, San Marino, Calif.
Helen Dickerson Heinen, 2376 East 71st Street, Chicago, Ill.
Charles W. Ihle, Jr., Suite 507, 100 North Phillips Street, Sioux Falls, S. D.
Charles Godwin Jennings, 356 Hillcrest Road, Grosse Point, Mich.
William R. Jones, 201 Doctors Building, Columbus, Ga.
Hilda Knobloch, University Hospital, Ann Arbor, Mich.
John Harry Lange, 104 Ponce de Leon Avenue, Atlanta, Ga.
John W. Leech, 429 Penn Avenue, Pittsburgh, Pa.
Conway Stone Magee, Gordon Building, Lake Charles, La.
Cornelius Shepherd Meeker, 222 North Genesse Street, Waukegan, Ill.
Alberta West Parker, 919 The Alameda, Berkeley, Calif.
Hugh W. S. Powers, Jr., 32 West Biddle Street, Baltimore, Md.
Donald T. Rendel, 5231 Holman Avenue, Hammon, Ind.
Mary L. Richardson, 2600 North Lawrence, Philadelphia, Pa.
Julius B. Richmond, 1819 West Polk Street, Chicago, Ill.
Harry Osbourne Ryan, 65 North Madison, Pasadena, Calif.
John W. Schonwald, 2206 MacArthur Boulevard, Oakland, Calif.
B. J. Siebenthal, 120 North Lafayette Boulevard, South Bend, Ind.
William A. Silverman, 175 East 79th Street, New York, N. Y.
Benjamin Spritz, 1755 Beacon Street, Brookline, Mass.
Paul Stone Strong, 1033 Gaylay Avenue, Los Angeles, Calif.
John Dudley Tobin, 701 Kenwood Parkway, Minneapolis, Minn.
David F. Weaver, 1008 First National Bk. Building, Davenport, Iowa
Ross R. Weller, Suite 310, Carpenter Building, Milwaukee, Wis.
Alvin DuBois Wert, 1020 South West Taylor Street, Portland, Ore.
William Kerr Zollinger, 1838 Parkwood, Toledo, Ohio
Ralph L. Zucker, 2318 Monroe Street, Toledo, Ohio

CANDIDATES EXAMINED IN BUFFALO, MAY 10 AND 11, 1947

Ruth Virginia Berney, 16 Lyons Avenue, Newark, N. J.
Nils William Bolduan, 1515 State Street, Santa Barbara, Calif.
Erika Bruck, Childrens Hospital, 219 Bryant Street, Buffalo, N. Y.
Robert Stewart Cleland, 136 North Madison Avenue, Pasadena, Calif.
John Henry Dale, Jr., 525 East 68th Street, New York City, N. Y.
John N. DeHoff, 147-05 Roosevelt Avenue, Flushing, N. Y.
Carl Drayer, 1756 Ocean Avenue, Brooklyn, N. Y.
Anne Mary Drislane, 758 Madison Avenue, Albany, N. Y.
Milton Carl Fleish, 461 Cornwall Street, Hartford, Conn.
James T. Fowler, United States Naval Hospital, Bethesda, Md.
Lewis M. Fraad, 525 East 68th Street, New York City, N. Y.

Kate M. Freund, 115 East 89th Street, New York City, N. Y.
Bernard German, 2 Shanley Avenue, Newark, N. J.
Richard H. Godwin, 53 Dorchester Road, Rockville Centre, N. Y.
Bernard Greenberg, 681 Ocean Avenue, Brooklyn, N. Y.
Clifford, G. Grulee, Jr., Pediatric Dept., University Hospitals, Minneapolis, Minn.
Francis Woodrow Helfrick, Castaner, Puerto Rico
Samuel Fredrick Jenkins, 231 West 139th Street, New York City, N. Y.
Neil Fremont Lebhar, Ray Street, Westport, Conn.
Maurice Lenarsky, 380 Riverside Drive, New York City, N. Y.
William I. Levinstein, 1125 Monroe Avenue, Rochester, N. Y.
Philip Frederick Lustbader, 577 Eastern Parkway, Brooklyn, N. Y.
Simon B. Mendelsberg, 1755 East 13th Street, Brooklyn, N. Y.
Eleanor Kellogg Peck, Stoneridge, Cedarcliff Manor, Poughkeepsie, N. Y.
Benjamin Reder, 38 Rock Street, Fall River, Mass.
Edward L. Robinson, 224 High Street, Hamilton, Ohio
George David Rook, 114 East 54th Street, New York City, N. Y.
Martha L. Smith, New York Hospital, New York City, N. Y.
Mildred Stanley, Peoples Bank Building, Tyler, Texas.
Henry B. Strenge, Strong Memorial Hospital, 260 Crittenden Boulevard, Rochester, N. Y.
Douglass W. Walker, 724 Main Street, Laconia, N. H.
Irving Bernard Wexler, 1672 Ocean Avenue, Brooklyn, N. Y.
Henry Hareus Work, Jr., 155 Hughes Street, Buffalo, N. Y.

Book Reviews

Manual of the Common Contagious Diseases. Philip M. Stimson, M.D., ed. 4, Philadelphia, 1947, Lea & Febiger, 503 pages, 67 illustrations, 6 color plates.

This fourth edition of Stimson's well-known text is an unusually complete revision and some fifty pages larger than the third. Many new developments in treatment, prophylaxis, and diagnostic measures have taken place in the field of the contagious diseases since the third edition in 1940, some the direct result of war medicine. All of these, including the use of the newer antibiotics, are incorporated in the new text. The chapter on poliomyelitis has been completely rewritten and enlarged and is of unusual importance, due to the marked increase of poliomyelitis in the last two years. It is a book not only of value to the student but of great value to the practitioner, as all of the newer accepted knowledge of the common contagious diseases is presented in a clear, direct manner.

B. S. V.

Psychiatric Interviews With Children. Helen Leland Whitmer, New York, 1946, The Commonwealth Fund, 443 pages. Price $4.50.

This book is one of many worthy byproducts resulting from the Commonwealth Fund's interest in psychiatry. It has twofold merit for the pediatrician. It describes at length, through the explanatory introduction and notes of the editor as well as through presentation of ten detailed case reports, what constitutes psychotherapy of children as practiced by teams of individuals in the setting of child-guidance clinics. The pediatrician who wonders what is going on within the walls of such a clinic, what is "happening" there to the patient that he has referred, will find answers in the pages of this book.

Probably of greater educational value to the physician who treats child patients and their parents, is the section on "Relationship." By this is meant the interplay of forces between psychotherapist and patient, which is considered the essence of dynamic therapy. The physician will learn much of value from this chapter if he substitutes in his reading the title "pediatrician" wherever the name "psychotherapist" appears. Resulting from this substitution should come insight as to the psychological role every doctor plays in relationship to patients. This element of patient care is seldom taught in the ordinary process of medical education, yet it constitutes a fundamental and basic principle in all treatment. Although the book is addressed primarily to students and practitioners of child psychiatry, it will stimulate as well as inform the pediatrician who is becoming increasingly interested in and practicing psychotherapy in his physical management of children and their parents.

SENN.

The Pharmacopoeia of The United States of America. Ed. 13, Easton, Pa., 1947, Mack Publishing Co.

This is the thirteenth revision of the United States Pharmacopoeia since its first publication in 1920, and was authorized by the U.S. Pharmacopoeal Convention held in 1940. There are approximately 100 additions and 120 deletions. Included in the additions are such agents as penicillin, typhus, and yellow fever vaccines, and diphtheria and tetanus toxoids. Tincture of Iodine 7 per cent has been deleted, and the mild (2 per cent) tincture of the earlier editions is retained as Iodine Tincture.

The most striking change is the use of the English titles for therapeutic agents in the leading position, and the rearrangement of the order on this basis. Latin titles are retained but made secondary. In 1828 an entire edition was published in Latin. The Pharmacopoeia has also adopted the tables of metric doses with approximate apothecary equivalents which were recently adopted by The National Formulary and New and Nonofficial Remedies, which simplifies prescribing.

Sex Education: A Guide for Parents, Teachers, and Youth Leaders. Cyril Bibby, M.A., M.Sc., F.L.S., New York 1946, Emerson Books, Inc., 311 pages, Price $2.50.

There has been no more perplexing problem to the parent, educator, and physician than that of sex education. Everyone is in agreement that sex education is not only desirable but necessary, but the questions of just what it should consist of and how and by whom it should be taught are far from being settled. There is no other subject in which there has been so much "passing the buck." Most parents and educators have little sound factual knowledge or information to form the basis of good instruction, while physicians are to a large extent limited to didactic physiologic instruction which is only one phase of sex education. Others approach it from the very unsatisfactory side, so far as education is concerned, of morals. On the one hand there is the danger of minimizing the importance of the subject and on the other the danger of overemphasis by the fanatical social hygienist. It is a most common experience for the physician to be asked for "books on the subject." Over a period of years we have had to reach the conclusion that, unfortunately, there was no really satisfactory book on the subject, and, further, that sex education, except, perhaps, for a few specific physiologic phases, is not a matter for formalized instruction or a "course," but is something that must be integrated with the entire life of the child from the preschool age to maturity. Recently, a book on sex education by an English author, Cyril Bibby, Education Officer to the Central Council for Health Education, came to our desk, which we feel is the sanest text on the subject which has as yet appeared. It should be of great value to the parent and teacher. Feeling we might be prejudiced in favor of the book because it expressed so well the ideas the reviewer had rather vaguely reached as a pediatrician, we gave it to the headmaster of a secondary school for his opinion. His comments not only coincide with the opinion of the reviewer but express so well the theme of the book that we quote them.

Dear Dr. Veeder:

To my mind the distinctive quality of Bibby's *Sex Education* is its sanity. Bibby sees sex education as a continuous process from the cradle to the grave, with schools as only one —but that a very important—educational influence.

I am impressed by Bibby's vision and understanding of the picture as a whole, by his forthright honesty, by his imaginative ingenuity in pointing out ways in which sexual knowledge and attitudes can be introduced naturally in a variety of school courses. At the same time he is obviously sound in pointing out the different types of instruction which are appropriate at different age levels. That he can include specific, detailed suggestions and not become dogmatic is to my mind a tribute to his skill. The many questions and answers in the closing chapters of the book are perhaps more numerous than a good teacher needs; and even these questions, in all their detail, will hardly make an unsuccessful or mediocre teacher successful.

In my judgment, the book does about all that a book can do. As you know, it develops the thesis, so far as schools are concerned, that the way to impart knowledge of sex is in a natural and normal way whenever it arises in school courses and in school relationships. It deals, as well, with suggested training to make teachers more skilled in their teaching of it. We are left with the limitations of teachers as human beings—and those limitations are very real. The book is a sensible, useful approach to a "hot" subject, discussion of which is too often surrounded with an atmosphere of taboo and morbid curiosity.

I have put the book in our faculty room for faculty reading, and I plan to have the faculty discuss means of adopting some of its suggestions when we take up questions of our curriculum and teaching in coming faculty meetings.

Sincerely yours,

(Signed) ROBERT CUNNINGHAM.

B. S. V.

Editor's Column

WHAT DO OUR READERS WANT OF THE JOURNAL?

WITH this issue, THE JOURNAL OF PEDIATRICS begins its sixteenth year. When it was started fifteen years ago, many told the Editor that there was no place nor need for another American pediatric journal and prophesied that it would not survive. They failed to realize the developments and progress that were taking place in pediatrics, both in medical practice and in medical education. These fifteen years have shown that there was a place for the JOUNAL, for it has attained a greater circulation and readership than any other pediatric journal in the world.

During these years, from an editorial standpoint, the JOURNAL has attempted to hold to a middle ground, so to speak, printing, on the one hand, some of the results of the research in our splendid American pediatric departments upon which progress ultimately depends, and, on the other, more popular clinical material of interest and value to the practicing pediatrician, who has little time for study and reading and who asks for something practical to help him in his daily work with children. At times it has been difficult to hold to a proper balance. From some the complaint has been that the JOURNAL was too "high brow," but from others has come the complaint that it was too "low brow." Sometimes we have been dissatisfied with this "straddle." Our own feeling is that the time has arrived when there is a need and place for two quite different types of American pediatric journals—one, highly scientific in character, presenting the results of research, part of which, while of value, has no direct bearing on pediatric practice, and the other, a journal of character and scope of particular interest and value to the man in practice. This latter we feel should be the ultimate direction which THE JOURNAL OF PEDIATRICS should take. Until a new type of scientific journal is established, the JOURNAL will continue, as in the past, to open its pages to the reporting of a certain amount of research studies. Despite the fact that today, as contrasted with fifteen years ago, many hundreds of young doctors have been trained and certified as pediatric specialists, only approximately 20 per cent of the children in the United States receive their medical care from pediatricians in private practice and in hospital and clinic work. Over one-half of the subscribers and readers of the JOURNAL are not pediatric specialists. The JOURNAL has a responsibility to these men and the children of America.

An astute colleague recently asked if the JOURNAL had ever made any effort to find out what its subscribers and readers wanted. We, rather shamefacedly, had to say no—that its editorial policies in the past had been determined by the editors and Editorial Board. In other words, the readers had to take what the Editorial Board decided to give them. It started us thinking, and this is the

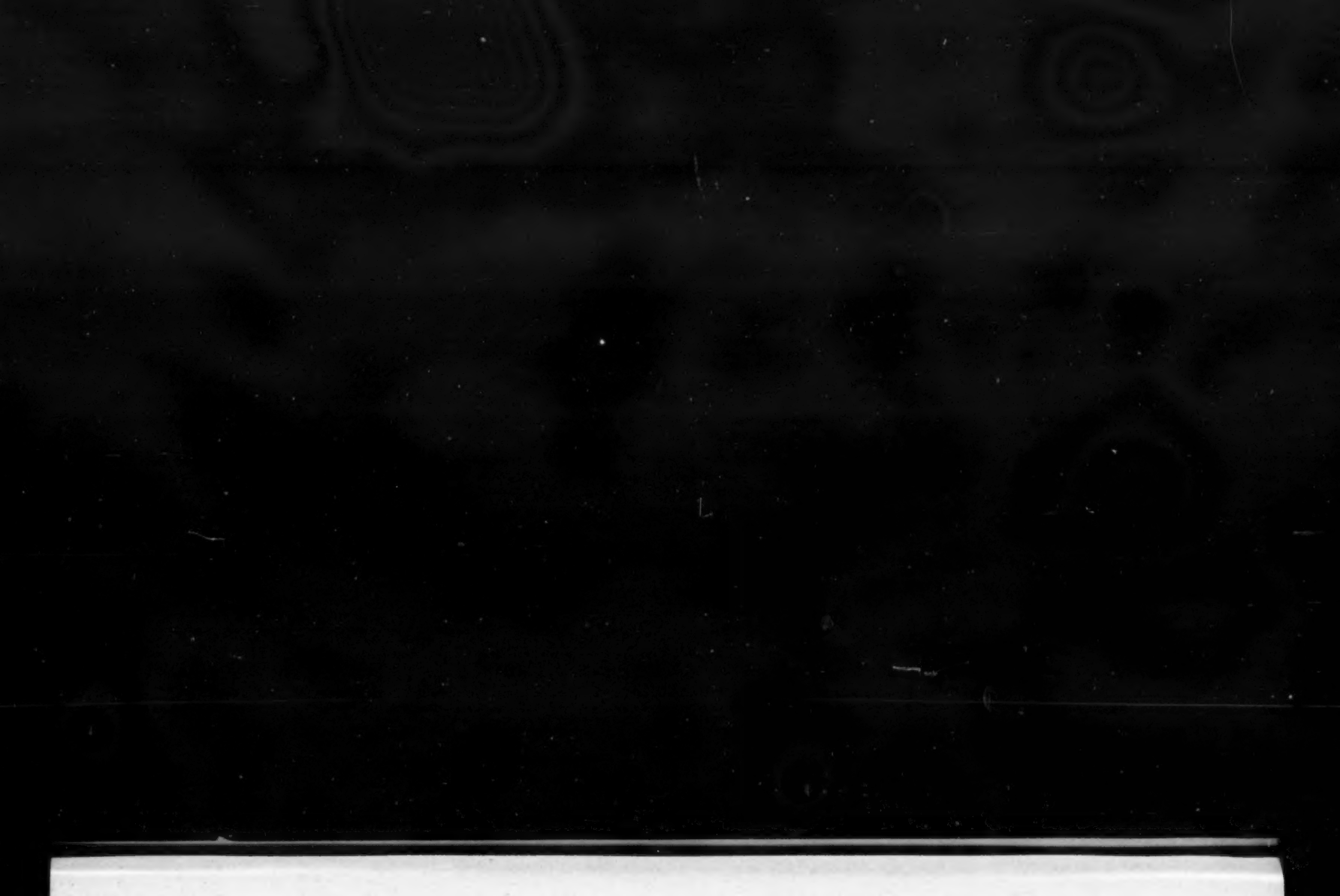
result. The editor would like to know how the readers feel about the editorial policies of the JOURNAL, what criticisms they have, and, more important, what suggestions they have to offer for its improvement.

A little over a year ago a department called "Social Aspects of Medicine" was started which has tried to present facts and ideas regarding this moot subject. Both the radical and conservative sides have had full opportunity for statements. It is not and never has been a propaganda column. A few months ago we started placing case reports in a special department printed in 10 point solid type, rather than the customary small 8 point. In this issue we are experimenting with two new departments, and we would like comment on their desirability and value to the reader. One, for lack of a better term (and perhaps you can suggest one), we term "Medical Care." If it proves of interest and value, it is our thought to present an article each month on some phase of pediatric practice which will tell in a direct, straightforward way how to handle or do it in practice. To start the department, in this issue, Dr. Philip M. Stimson, a recognized authority on the subject, discusses the treatment by the pediatrician and practitioner of poliomyelitis in its acute stage. Another department with which we plan to experiment is entitled "Clinical Conference." Many of our hospitals hold weekly conferences or "grand rounds," in which the everyday run of hospital material is presented and rather extemporaneously discussed. Many of us plan our trips so as to attend these conferences as we visit various cities. For this issue, Dr. Alexis Hartmann at the St. Louis Children's Hospital consented to have one of his weekly conferences recorded on a Soundscriber and transferred to print.

The JOURNAL, after fifteen years of growth, finds itself in a position to experiment editorially, and to change and develop along new lines in an attempt to be of greater value and interest to its readers. As a first step, we are asking our readers to tell us what they like or dislike about the editorial policy of the JOURNAL, what they want continued or changed, what they feel about these new departments, and what suggestions they have which would make the JOURNAL of more value and interest to them. In other words, we want to do what, perhaps, we should have done before, and what a good industrial manager would do—try to find out what the consumer wants.

The publishers, The C. V. Mosby Company, have never interfered with or attempted to influence the editorial policy of the JOURNAL in any way. They are continuing the same policy.

We would appreciate hearing from you.

BORDEN S. VEEDER.

3720 Washington Ave.,
St. Louis 8, Mo.